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MOLD FUNGI IN THE ETIOLOGY OF RESPIRATORY ALLERGIC DISEASES

X. Intrinsic Fungus Factors in Relation to Asthma

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PREVIOUSLY I have offered some remarks upon a device used by me to discover certain types of allergic clinical patterns due to fungi. Briefly, this device consists of routine culture of the sputum of asthmatic patients by methods designed to facilitate the growth of fungi and the clinical and immunological evaluation of the significance of the strains isolated.

The technique of the method is simple and brief. In the course of study of the sputum from asthmatic patients, careful attention is paid to the recognizable fungus elements which might be seen on wet mounts and stained preparations. In addition, cultures are done by the spot method on Sabauraud's agar, using 30 to 50 spots to a Petri plate surface. These spots should be inoculated by touching the surface with a loop of sputum but avoiding streaking. If the loop contains a large amount of inoculum it may be touched two to four times to the surface. The loop should be resterilized and a sample selected from a different portion of the specimen, making sure that all portions are sampled which present different gross characters. Adequate sampling is important. The usual bacteriological technique designed to select only the portion of the specimen likely to arise from a pathological lesion and to contain pathogens must be avoided. The object here is to discover the possible presence of fungi from any part of the respiratory tract quite apart from it's pathogenicity in the usual sense. The plates are sealed to prevent drying and incubated at room temperature for two to three weeks. Most positive specimens show recognizable growth within the first week.

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In general, those specimens which yield no more than one or two colonies of fungi are not considered further unless the clinical course suggests a restudy at some later date, as will be detailed below. Specimens which yield growth of fungi in 50 per cent or more of the spot inoculations are earmarked for more complete study. This criterion is only arbitrary as it is apparent that by improper sampling one may obtain either no fungi or 100 per cent growth in the spots from specimens in which the distribution of organisms is scattered.

Only occasionally does one encounter a specimen which yields more than one strain of fungus. Also only on rare occasions have fungi of pathogenic significance been found.

Recently an additional method has been employed to secure samples for culture. This has been the use of nasal swabbings or washings for culture and has been employed too few times to permit evaluation of its usefulness.

Admittedly, by this procedure, one will encounter numerous specimens from which fungi may be isolated which prove to be without significance. It is necessary, therefore, to adopt some criteria by which to select those on which more careful study is to be done. These criteria are:

1. A yield of 50 per cent or more growth in inoculated spots.

2. A repetition of positive findings, although variable in percentage of positive spots, in specimens collected at intervals of several days and repeated with three to six specimens.

3. A yield of any fungi in specimens from patients who have presented no evidence of other more commonly recognizable etiological factors.

4. A yield of fungi variable in percentage of growth from zero to 50 per cent or more, as observed in multiple specimens, the percentage of growth varying in direct proportion to the intensity curve of the patient's symptoms.

5. A yield of growth of any proportion in patients whose x-ray findings suggest the possibility of a primary fungous infection.

6. A yield of growth which on initial study is minimal in proportion but is isolated from a specimen suggesting a bacterial etiology, and which increases to maximal proportions following antibiotic therapy, which fails to improve or even intensifies the clinical symptoms.

To these criteria, of course, must be added the general consideration that more common etiological probabilities should be explored, as usual, by history, skin testing and experimental trial.

After it is decided that consideration must be given to the possible etiological significance of the strain of fungus isolated, the organism is isolated in pure culture, grown to maximal concentration in an acid, high-sugar-content broth. The broth is decanted, filtered and preserved. The mat of fungous growth, without preliminary drying, is extracted with a

saline extracting fluid for forty-eight hours, then is filtered and glycerine is added in equal proportions.

These two products are then used to do skin tests, using sterile broth as a control. Cutaneous tests are done first with the undiluted broth and extract. If negative results are obtained, intracutaneous tests are then done, using ascending strengths, beginning with dilutions of 1:1,000 and increasing to undiluted broth and 1:10 dilution of the glycerinated extract. Controls of similar dilutions of broth and glycerinated extracting fluids are used. If positive reactions are obtained, passive transfer sites are prepared and tested.

If clinical and mycological evidence is suggestive and the skin tests are positive, treatment is then carried out essentially as in pollen therapy. It is not felt that the failure of passive transfer is a contraindication to therapy.

With such extracts it has been possible to produce an exacerbation of symptoms and/or urticarial systemic reactions. Improvement in the clinical picture in a small but significant proportion of patients who had otherwise presented the clinical features of intractable asthma has been obtained.

Clinically these patients may be separated into three fairly definite categories.

First, an occasional patient will present the necessary mycological findings together with x-ray or other evidence of pulmonary fungus disease.

Such a case is that of Mrs. P. This patient, aged forty, had had definite allergic episodes of flexural dermatitis and urticaria previous to the onset of asthma. The asthma had been present for two years at the time of the initial study. During these two years, symptomatic treatment, skin testing, trial dieting and history had failed to indicate the possible etiology or to relieve the patient of her symptoms.

Cultural studies, as outlined above, gave heavy growth of a Monilia type fungus. X-ray studies revealed a patchy, atypical infiltrative reaction considered to be probably of mycological origin.

Skin tests with extracts were considered to be significantly positive. Treatment was instituted by hyposensitization, and marked improvement in asthmatic symptoms was obtained after about three months. However, the productive cough, positive cultures and x-ray findings remained essentially as described. Therapy was then directed to the primary disease, chiefly by repeated courses of iodides and deep x-ray. Gradually the symptoms subsided over a period of three years, and eventually the sputum cultures became negative for Monilia.

Only two other cases essentially similar to this have been seen. In this type of case, one must emphasize the protracted and intensive nature of the therapeutic approach to finally achieve success.

The second fairly definite category into which these patients may be placed is that in which symptoms are fairly constant, cultural findings are likewise constant, and no evidence of infiltrative lesions or other evidence of pulmonary fungus disease exists. One can well postulate that these cases are examples of intrabronchial parasitic but nonpathogenic

fungus infestations to which the patient has become allergic, with resulting asthmatic symptoms.

Such a case is that of Mr. T., aged twenty-four. Five years previous to the initial study he had experienced a protracted "cold which had developed into flu-pneumonia" (this is the patient's description). The nature of this initial illness is, of course, obscure. Following several months of cough, asthmatic wheezing developed which, although paroxysmal, occurred almost daily. The usual history and skin tests failed to reveal significant findings. Cultures produced about 50 per cent spot growth of a fungus which was not identified except that the usual pathogenic types were excluded. Identical findings were obtained on four sputum specimens, studied at intervals of four days. Extracts gave large typical skin reactions by the scratch test. Treatment was strikingly successful. Symptoms subsided rapidly. After two months, no further asthma occurred. Slight cough with minimal production of sputum persisted for six months. Cultures taken at intervals during treatment showed gradual decline in the number of positive spots, and no growth was obtained after the fifth month. The patient was well six years after first seen—five years after treatment was discontinued.

Twenty patients have been seen essentially similar to this. Results have been strikingly good in nine of these, helpful or fair in five, and failures in six.

The third group of patients consists of those in whom symptoms are paroxysmal and the history suggests some environmental factor as the offending one. Cultures show sporadic growth of fungi. Other etiological factors are excluded by test or therapeutic trial.

Such a case is that of Mr. B., aged twenty-six. This patient was the coach of a high school football team which practiced daily on a Bermuda-grass playing field. During his second season on this field, asthma began to occur during the practice session. This was the first recognized allergy in this patient. It seemed obvious that Bermuda sensitivity was the most logical offender in this case. However, scratch and intracutaneous tests to Bermuda pollen were negative. Also the season of pollenation had terminated, and the grass was in a dormant state. Exposure to other Bermuda stands (a golf course ten miles distant from the football field) failed to induce asthma. This puzzle resolved itself after finding a heavy growth of an Alternaria type fungus from the nasal washings obtained shortly after being on the field. Examination revealed a heavy parasitization of the dead Bermuda leaves and stolons by Alternaria. Skin tests with our routine Alternaria extract gave a mild suggestive reaction by intracutaneous test. An extract prepared from the Alternaria strain isolated, however, produced a maximal reaction, by scratch test, 3 inches in average diameter, and an attack of asthma which required control with adrenaline for six hours. Therapy was not attempted in this case. By this time our studies were completed, the football season was over, and the following year the patient changed his work to avoid contact with the offending agent.

Another case of interest in this group is that of Miss Y., aged twenty-two. This patient presented herself with a complaint of seasonal hay fever of summer and fall type, of several years' duration. Symptoms coincided sharply with the grass and weed seasons of her locality, and this was confirmed by satisfactory skin tests, positive reactions being obtained to Bermuda, Russian thistle and Palmer's amaranth. Hyposensitization was instituted coseasonably, with minimal doses in August, and relief of symptoms occurred within two weeks following institution of treatment.

Due to the very long combined grass and weed season in our locality (May to mid-November), perennial treatment was carried out, with gradual increase of dose to near tolerance during the year following the first season. The second season's results were excellent. No asthma occurred and only occasional mild hay fever occurred. Following this season the patient discontinued treatment. The third season, under observation but with no treatment, justified the patient's decision to omit treatment, as no symptoms occurred. This excellent state of affairs continued during the fourth season, until late October when she presented herself again with marked asthmatic symptoms and cough which produced a clear mucoid sputum without pus but with many eosinophiles. This seemed to be such a clear-cut example of return of symptoms following two seasons without treatment that her first pollen mixture was used to immediately institute coseasonal therapy. However, her sputum had been processed routinely, and it was surprising to me when a yield of 80 per cent positive growth of a fungus was found after several days. On maturity this was found to be an Alternaria type strain. It was then recalled that on the first skin testing the patient had given a 4-plus reaction to Alternaria. This fungus had not been included in her initial treatment mixture, however, because of the sharp coincidence of her symptoms with the grass and weed seasons, and the experience that all previous cases of Alternaria clinical sensitivity seen in our locality had presented perennial symptoms with a marked spring (previous to grass season) and late fall peak.

Another sputum specimen was examined by digesting the tenacious mucus with caroid powder and centrifuging. The sediment showed the presence of a moderate number of Alternaria spores but no evidence of mycelial formation. Questioning revealed that the first symptoms of cough and asthma for this recurrence had occurred while the patient had been gathering beans from her family's commercial truck garden. (This had been her occupation throughout the course of our contact with the case.) Some of the leaves from these bean plants were examined and found to be heavily parasitized with Alternaria.

A re-check of the skin test again showed a strong positive scratch test, and passive transfer was definitely positive. These tests were done with a stock Alternaria extract. In this case, extracts were not made from the strain isolated from the patient's sputum.

Treatment of this case consisted of a few minimal doses of Alternaria extract and strict avoidance of the parasitized bean patch. The asthma and cough subsided promptly and treatment was discontinued by the patient's choice. Two years later, when last contacted, the patient continued free of asthma and hay fever.

Another case of interest, but not fitting into any clear-cut group, is that of Mrs. B., aged thirty-six. This patient was first seen four years ago with a long history of asthma which had begun following a respiratory infection of unknown nature. She was extremely underweight and presented the symptoms of a paroxysmal cough which raised copious quantities of purulent sputum. There was paroxysmal dyspnea of nonasthmatic type. X-ray and physical examination indicated a diagnosis of bronchiectasis and bronchitis. There had been many studies, by physicians in many cities, done on this patient with exhaustive skin tests and trial dieting. There had been many periods of hospitalization. She had been placed on morphine, with resulting addiction, and when first seen was taking 3 grains daily. She rebelled at the suggestion of further hospitalization. The outlook for therapeutic success with her was indeed gloomy. Study was undertaken in a half-hearted manner, both on my part and on the part of the patient. Routine studies on the sputum revealed neutrophilic and eosinophilic cytology with a predominating bacterial growth of nonhemolytic streptococci. Sabauraud's plates showed two colonies of Monilia.

For a year, therapeutic attempts consisted of efforts to minimize the inflammatory process by the usual means—all of which had been attempted before. She continued to present all of her symptoms and continued in the use of narcotics. Repeat sputum cultures continued to reveal the same findings as outlined above, with no variation in the Monilia contents.

At this juncture we first began the use of penicillin by the aerosol method. The patient was persuaded to submit herself to a trial of this and was forced into the hospital by the refusal to furnish further narcotics. The aerosol was begun with the use of 20,000 units of penicillin given five times daily. Within four days there was a marked reduction of the amount of sputum and a change in its character from purulent to mucoid. However, the cough continued to be troublesome, but no asthmatic wheezing was heard. As withdrawal of narcotics was being attempted and the patient was extremely wilful and headstrong, the cough was discounted—especially as the physical findings had improved: the low grade fever had subsided, and there had been a significant gain in weight. After six weeks of hospitalization, narcotics had been successfully withdrawn and there had been a marked improvement in all aspects of the case, except the continued cough (much less intense) and mucoid sputum. The aerosol had been gradually reduced in frequency, and the final week only two inhalations had been given. Re-study of the sputum at this juncture showed an almost total absence of coccoid flora. No replacement by B. coli or other bacterium was found. However, the microscopic and cultural findings indicated a passive population of a Monilia-type fungus. Skin test with stock Monilia extracts was positive—both immediate and delayed—by the intracutaneous technique. Passive transfer was negative. Before autogenous extracts could be prepared, the patient was dismissed from the hospital. She made a trip to another city, and her stay proved to be permanent. Through acquaintances it was learned that after several months she began to decline and was again under medical care.

DISCUSSION

We believe that the methods outlined above offer valuable aid in the management of a selected, though significant, group of intractable asthmatic patients. Admittedly there are many deficiencies in these studies. Passive transfer has been attempted in only one-fourth of the cases seen. It has been positive, however, in six of the eight attempts. Many cases have been encountered giving a few colonies of fungi which have not been studied more completely to evaluate their significance. No attempt has been made to evaluate these findings statistically. As I have previously said, from the patient's viewpoint his own problem constitutes 100 per cent of his interest. Nor has any attempt been made to identify beyond simple type grouping the strains of fungi encountered. As this work has all been done in private practice, those familiar with the difficulties of mycological study can readily appreciate the reason for that omission.

From my experience, which has extended over sixteen years with this type of study, I feel convinced that several reliable conclusions can be drawn. First, it seems apparent that the source of fungus exposure may reside within the respiratory passage without there being recognizable infiltrative pathologic conditions associated with them. Under such conditions it also seems possible for these fungi to behave as to other allergens.

The use of this type of study will occasionally detect a fungus spore

etiology in patients exposed to an otherwise unsuspected heavy concentration of fungi.

In one case detailed above, only small questionable skin reactions were obtained with stock extracts, while maximal reactions and systemic reactions were obtained with autogenous extracts. This may be due to one of several possibilities. Identical species of fungi may vary widely in antigenicity from strain to strain. Or closely related species which do not present identifiable features on superficial study may exist and give some cross reaction due to antigenic similarity or to the presence of multiple antigens of varying nature. A third possibility is that the method of extracting fungi outlined above yields products of much more antigenic potency than those obtained by the widely practiced method of drying and washing fungous growth before extracting. One must admit, of course, that extracts prepared as outlined above would be impossible to duplicate and difficult to standardize. On the other hand, fungi which are dried and washed, defatted and otherwise treated before extraction are probably denatured in an undetermined degree. We have additional evidence to suggest that this latter statement is probably correct. It also seems apparent from the last case detailed above, plus two additional cases not here reported but of similar findings, that effective antibiotic aerosol therapy may permit the abundant overgrowth of a fungus present in only minimal amount previous to treatment. The significance of this has not been evaluated but is now under study.

MOLD FUNGI IN THE ETIOLOGY OF RESPIRATORY ALLERGIC DISEASES

XI. Phytopathogenic Fungi in Aerobiological Populations

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THE SUBJECT of fungi in relation to inhalant respiratory allergy has become recognized by physicians, mycologists, plant pathologists and others whose interests extend into this field. It has been definitely established that many of these fungi are carried in the air from infected plants in the case of phytopathogens and from their several sources in the case of saprophytic forms. The relatively small number of reports on phytopathogens may be due in part to the fact that in many of the surveys which have been conducted, the agar plate method was used; consequently, the obligate parasites were missed. It is probable also that in many studies where the slide method was employed, spores of phytopathogens were overlooked. Interested workers cannot but recognize that many problems are open for investigation. Much information is needed on the fungi in the role of allergens. But before this phase of the problem, which is a clinical one, can be studied adequately, more information is required concerning the fungi themselves. This is particularly true of the fungi which cause plant disease. It would simplify matters, indeed, if, when a source of infected plant material is located in a given environment, it could with some certainty be identified as a potential source of allergenic material in the air population in that locality, or as surely be ruled out. It seemed desirable, therefore, to conduct a series of studies in this laboratory which would contribute to the particular problem of phytopathogens and their possible role as allergens.

The studies were planned for the purpose of finding out what relations exist between fungus-infected host plants in a given location and the air population at that location, and at near and farther distances from the host symptoms within an area of approximated limits or outposts. One objective was to determine if host symptoms of a particular plant disease in a given location are an index to air-borne spores of that particular pathogen; that is, if fungus-diseased plants are located, does it follow that spores of the pathogen are carried aloft and will be encountered in the air population at this location? Specifically, can one expect to find Dichondra rust spores on slides exposed in this vicinity, if rust-infected Dichondra turf is located? In other words, might Dichondra turf indicate a possible source of allergenic material in cases of inhalant respiratory allergic diseases?

A second objective was to determine whether those spores which are

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known to be carried aloft at the host infection site are also carried away from the infection sites, and if possible, to what distances, that is, within the outposts. Specifically, if the spores of the powdery mildews are carried aloft and are encountered in the air population at the infection site, might they be expected also to be recovered as air constituents ten city blocks distant from the host symptoms? In other words, might the spores of powdery mildew on crape myrtle on the University campus be expected to be encountered on slides exposed on San Antonio Street, and thereby constitute a potential source of allergenic material for residents there who do not frequent the campus?

A third objective was to determine whether spore incidence in the air is seasonal, and if so, if it corresponds with the seasonal aspects of host infection. Specifically, are there peaks for spore concentration of plant pathogens as air constituents, and if so, do these peaks correlate in any way with the intensity of the host symptoms? In other words, is there a Bermuda grass smut "season" or a Johnson grass smut "season," and might one expect to find Johnson grass smut in the air in December after frost has killed the hosts? The answers to any one or all of these would be specific, yes, or no, but would have to be determined individually for each phytopathogen under investigation.

The Austin region provides hosts for at least three well-known and economically significant plant diseases, namely, rusts, smuts, and powdery mildews. These include those pathogens most commonly referred to in the literature of aerobiology, the smuts and rusts, as well as those mentioned infrequently or not at all, the powdery mildews.

For the purpose of the studies, smuts of Johnson grass and Bermuda grass, rusts of Johnson grass and Dichondra, and powdery mildews of crape myrtle, Evonymus and wild China were selected and designated as "selected pathogens."

1. Johnson grass smut, *Sphacelotheca sorghi* () Clinton on Johnson grass, *Sorghum halepense* () Pers. ("covered kernel smut").
2. Bermuda grass smut, *Ustilago cynodontis* P. Henn on Bermuda grass, *Cynodon dactylon* () Pers. ("covered smut")
3. Johnson grass rust, *Puccinia purpurea* Cooke on Johnson grass, *Sorghum halepense* () Pers.
4. *Dichondra* rust, *Puccinia dichondrae* Mont. on *Dichondra caroliniensis* Michx.
5. Powdery mildew, *Uncinula australiana* McAlpine on crape myrtle, *Lagerstroemia indica* L.
6. Powdery mildew, *Microsphaera alni* Wallr. on *Evonymus* sp.
7. Powdery mildew, *Uncinula circinata* Cke and Peck on wild China, *Sapindus drummondii* H. and A.

Johnson grass smut, Dichondra rust, powdery mildew on crape myrtle and on Evonymus appear more or less simultaneously in early April; Bermuda grass smut appears in early June, powdery mildew on wild China the first week in July, and Johnson grass rust sometimes later in July. In the

case of the smuts and rusts, superficial symptoms of infection are diminished to the point that the host plants appear normal following mid-July, but symptoms reappear in the fall. The powdery mildews do not show this seasonal variation.

Characteristic spore types (including chlamydospores in the smuts, urediospores in Johnson grass rust, teliospores in Dichondra rust, and conidiospores in the powdery mildews) have their own identifying features and can be recognized with certainty. This holds for the conidiospores of the different powdery mildews.

Locations or areas of infected hosts were designated as "infection sites." "Respective sites" and "corresponding sites" were used for specific pathogens. The sites chosen were located on or near the campus of The University of Texas and are representative of infection areas in the Austin vicinity. These are included in an area comprising some twenty-five to thirty blocks which pass through a portion of the campus from one residence section to another.

Site 1. Smut-infected Johnson grass. Home Economics Building, north, east.
Site 2. Turf of Bermuda grass, smut-infected. Chemistry Building, north.
Site 3. Rust-infected Johnson grass. Waller Creek, east.
Site 4. Carpet of Dichondra, rust-infected. Hogg Memorial Auditorium, west.
Site 5. Powdery mildew-infected crape myrtle shrubs. Union Building, north; Hogg Memorial Auditorium, west.
Site 6. Evonymus hedge, powdery mildew-infected. Residence, 24th and San Antonio Streets.
Site 7. Powdery mildew-infected wild China tree. Union Building, east.

Samples of the air population were obtained on adhesive slides at "sampling sites" or "exposure sites." These were selected within 20 to 30 feet of heavily infected host plants for each of the pathogens, at levels representative of the air content with which sensitive individuals come in contact.

The period of investigation extended from April 2 to July 17, 1946. Slides were exposed daily in duplicate and allowed to remain in place for twenty-four hours. Supplementary surveys were made the following December and again in January.

The present paper is a separate and distinct one from a longer dissertation on phytopathogenic fungi in aerobiological populations, which is in manuscript, to be published soon in detailed form. Some of the facts and figures revealed in the studies, however, lend themselves to a short paper, and are presented in summary form, where, relieved of cumbersome details, results can be discussed to the point. Details of method, qualitative and quantitative tables and lists, figures, graphs, photographs, and other details, while invaluable for the record, are omitted here, as well as historic aspects, but all of these will have their place in the longer work, which will be a companion piece to the shorter paper. For the task of collecting a voluminous amount of data, special credit is due the junior author.

As indicated by their presence on slides exposed at the corresponding sampling sites, spores of six of the pathogens, the smuts, Johnson grass rust, and the powdery mildews are air-disseminated and apparently constitute a considerable fraction of the air population at the respective infection sites. These therefore would come into the "potential" category with respect to allergenic significance in inhalant respiratory diseases. Dichondra rust presents a unique and different picture. Spores were never encountered on any of the exposure slides, not even when the slides were placed under the infected plants. It would seem that these are not air-disseminated, and the plants therefore would be eliminated from the probability of allergenic significance.

Recovery of spores at the corresponding sampling sites would imply that these are carried short distances from the infected hosts in each case, at least the 20 or 30 feet representing the distance from infected plant to exposure site. This would seem to lend support for these in the potential category with respect to their allergenic significance.

Recovered only at the corresponding sampling sites, spores of Bermuda grass smut, Johnson grass rust, and the Evonymus and wild China powdery mildews are apparently limited to the immediate vicinity of the infected plants, and consequently have potential allergenic significance only in a local environment.

As indicated by recovery of spores at the various other sampling sites, which involved their being carried considerable distances in some cases, Johnson grass smut and crape myrtle powdery mildew would seem to have a more extensive range of dissemination, and consequently would have potential allergenic significance in wider environments.

Seasonal variation is strongly indicated for the smuts, less so for the rusts, and little or not at all for the powdery mildews. A continuing increase in spore numbers in the air generally followed an increase in host infection, whereas a decrease was noted when growth of the host was curtailed by unfavorable weather. In the case of Johnson grass smut, spores were recovered from the air after host symptoms had disappeared in the fall and winter. It would seem, then, that even after host symptoms are no longer present in a given environment for some phytopathogens, spores may continue to be present in the air and constitute a potential hazard for sensitive individuals.

Each plant disease poses its own problems. It has been shown that although in six of seven cases host symptoms indicate air-disseminated spores, there is the exception in Dichondra rust. Likewise, although spores are no longer encountered in the air after host symptoms have disappeared in five of six pathogens, there is the exception in Johnson grass smut.

The postseason aspect of Johnson grass smut as a component in the air population cannot be overlooked as having possible clinical significance.

Other points revealed by these studies appear in the long paper, the other air constituents encountered on the exposure slides being one of

these; numbers of the air components is another; whether the spores occur singly, in masses, chains, or other grouping, is another. The studies have been very revealing, and a considerable amount of data has been assembled.

Results of the studies, as indicated and discussed in this paper, have, however, added certain information in the nature of answers, at least in part, to the questions raised as objectives at the beginning of the investigation. First, spores of plant disease fungi do get into the air population by air dissemination; that is, spores of some phytopathogens are air disseminated. But since at least one of these is not, it can only be said that host symptoms are but potential sources of air-borne spores, which in turn may or may not have allergenic significance, and the diseased plants are therefore only potential hazards with respect to inhalant respiratory disease, but, as such, would of necessity have to be investigated in analyzing an environment.

Secondly, spores that are air disseminated may be carried distances near or far from the diseased plants. In the cases of some of these, the spores are confined to the air population near infected hosts; in other cases, the spores seem to be widely disseminated, and are found at greater distances from the plant hosts. Infected plants that constitute potential hazards in inhalant respiratory disease, then, fall into two groups: those that are concerned with local environments, and those having significance in wider environments.

Thirdly, for some air-borne phytopathogens, there is a "season," but for others, this is not indicated. For some, seasonal aspects are a reflection of host symptoms. For others, there is a "postseason" for the spores of the fungus after host disease symptoms have disappeared.

MOLD FUNGI IN THE ETIOLOGY OF RESPIRATORY ALLERGIC DISEASES

XII. Further Studies with Mold Extracts

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PREVIOUS studies by the Association of Allergists for Mycological Investigations[1] have indicated the superiority of an acetone-precipitated extract of *Alternaria tenuis* over antigens prepared by various other conventional and experimental methods. The work which forms the basis of this report was undertaken for the purpose of evaluating further this method of extraction, not only for Alternaria but for other commonly encountered molds of the dematiaceous group as well.

It might be recalled here that some of our earlier experimental extracts[3] were made from *Aspergillus niger* as well as from *Alternaria tenuis.* Eventually, however, after it was discovered that definitely positive reactions were not obtained frequently with *Aspergillus niger,* this species was abandoned for further studies in favor of *Alternaria tenuis,* which has a relatively high sensitization index. For like considerations, it occurred to us that since reactions to other dematiaceous molds are encountered with some regularity and often also when Alternaria reacts, a study of related molds would seem most logical. Also, if the technique should prove adequate for these other molds, not only would the merits of the method be enhanced, but some practical indication regarding criteria for evaluating multiple reactions in this group might be noted.

Accordingly, in the summer of 1947 glycero-saline extracts were prepared by our experimental Technique 33 (acetone precipitation) from *Hormodendrum cladosporioides, Helminthosporium interseminatum,* a Spondylocladium species, *Curvularia trifolii* and *Nigrospora sphaerica,* as well as from *Alternaria tenuis.* At the same time the nonprecipitated discard products resulting from the preparation of four of these extracts (Alternaria, Hormodendrum, Helminthosporium and Spondylocladium) were concentrated by evaporation and were prepared into extracts comparable qualitatively with the extracts of the acetone-precipitated fraction. All extractions were carried out simultaneously so as to minimize differences due to aging. The finished products were distributed to our collaborators for testing and neutralization experiments.

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TABLE I. DIRECT AND IN VIVO NEUTRALIZATION TESTS

Mold	Direct Tests				Neutralization Tests											
	Punch	Intradermal			Alternaria	Retest	Hormodendrum	Retest	Helminthosporium	Retest	Spondylocladium	Retest	Curvularia	Retest	Nigrospora	Retest
		1/100,000	1/10,000	1/1,000												
Patient 1 (Davies)																
Alternaria	+			++++	++++	−	+++	+++	+++	++	+++	+	+++	+	+	+++
Hormodendrum	+			++++	++++	−	++	−	+++	+	+++	−	+++	−	+	++
Helminthosporium	+			+++	++++	+	++	+++	+++	−	+++	+	+++	−	++	+++
Spondylocladium	++			++++	+++	+	++	+++	+++	−	+++	−	+++	−	++	+++
Curvularia	++			++++	++++	−	++	+	+++	+	+++	−	+++	−	++	++
Nigrospora	−			−	+++	−	++	−	+++	++	+++	−	+++	−	+	−
Control					+++		++		+++		+++		+++		+	
Patient 2 (Rowles)																
Alternaria	+	++	+++		++++	−	+++	++++	++	+++	++	++++	+	++++	++	++++
Hormodendrum	+	+	+++		++++	−	++++	−	++	+	++	++	++	++	++	−
Helminthosporium	−	+	++		++++	−	+++	−	+	−	++	−	++	+	+++	−
Spondylocladium	+	+	++		++++	−	+++	−	++	−	+++	−	+++	−	++	−
Curvularia	++	+	++		++++	−	+++	−	+++	−	++	−	++	−	+++	−
Nigrospora	−	−	−	+	++++	−	+++	−	+++	−	++	−	++	−	++	−
Control					++++		++		++		+		+		++	
Patient 3 (Keene)																
Alternaria	++		++		++++	−	++	++++	+++	+	++++	+	++	−	++	++
Hormodendrum	++		+		+++	−	++	−	+++	−	+++	−	+++	−	++	++
Helminthosporium	++		++		+++	++	++	+++	+++	−	+++	−	+++	−	+++	+++
Spondylocladium	+++		++++		+++	+++	++	+++	+++	+	+++	−	+++	−	+++	+++
Curvularia	−		++		+++	+++	++	+++	+++	+	+++	−	+++	−	++	++
Nigrospora	+		+		+++	−	++	−	+++	+++	+++	−	+++	+	+++	−
Control					++++		++		+++		++++		+++		+++	
Patient 4 (Hornbuckle)																
Alternaria	++		+++		++++	−	−	+++	+++	++++	++	++++	++	+++	−	++++
Hormodendrum	−		−		++++	−	+	−	++	−	++	−	++	−	−	−
Helminthosporium	+++		++		++++	−	−	+	++	−	++	−	++	−	−	++
Spondylocladium	++		+		++++	−	−	+	++	+	++	−	++	−	−	++
Curvularia	+		++		++++	−	+	−	+	−	++	−	+	−	−	+
Nigrospora	−		−		++++	−	+	−	++	−	++	−	+	−	−	−
Control					++++		−		++		+++		++		−	

TABLE I. DIRECT AND IN VIVO NEUTRALIZATION TESTS

TABLE I. DIRECT AND IN VIVO-NEUTRALIZATION TESTS

Mold	Direct Tests				Neutralization Tests											
	Punch	Intradermal			Alternaria	Retest	Hormodendrum	Retest	Helminthosporium	Retest	Spondylocladium	Retest	Curvularia	Retest	Nigrospora	Retest
		1/100,000	1/10,000	1/1,000												
Patient 5 (Bastian)																
Alternaria	+++		+++		++++	−	+++	++++	+	++++	+	+++	++	+++	++	+++
Hormodendrum	+		++		++++	−	++	−	++	−	−	+	+	+	++	−
Helminthosporium	+		+		++++	−	+	+	++	−	−	−	+	−	++	−
Spondylocladium	+		+		++++	−	++	−	++	−	+	−	+	−	+	−
Curvularia	++		++		++++	−	++	−	+	+	+	−	−	−	++	−
Nigrospora	−		−		++++	−	+	−	++	+	+	+	+++	−	++	−
Control					+++		++		++		++		++		+	
Patient 6 (Hicks)																
Alternaria	++		++++		++++	−	+	++	−	+++	−	++	−	+++	−	+++
Hormodendrum	−		+		+++	−	+	−	−	−	+	++	−	++	−	+
Helminthosporium	+		+		++++	−	+++	−	−	−	−	−	−	−	−	−
Spondylocladium	−		−		++++	−	++	−	+	−	−	−	+	−	−	−
Curvularia	−		−		++++	−	+++	+	−	−	+	−	+	−	+	−
Nigrospora	−		+		++++	−	+++	−	−	−	−	−	+	+	−	−
Control					+++		++		−		+		−		+	
Patient 7 (Crawford)																
Alternaria	+			+++	+++	−	−		++	++	+	+	+	++	−	++
Hormodendrum	+			−	++++	−	−		++	−	+	−	+	−	−	−
Helminthosporium	+			++	+++	−	−		+	−	+	−	+	++	−	+
Spondylocladium	−			++	+++	−	−		++	−	−	−	−	−	−	−
Curvularia	−			−	+++	−	−		+	−	−	−	−	−	−	−
Nigrospora	−			−	+++	−	−		++	+	+	−	+	+	+	−
Control					++				+		++		++		−	
Patient 8 (Gordon)																
Alternaria	+		+++		++++	−	+++	++++	+++	+++	+++	++++	+++	++++	−	++++
Hormodendrum	−		+		++++	−	+++	−	+++	−	+++	−	+++	−	−	−
Helminthosporium	−		++		++++	−	+++	−	+++	−	+++	−	+++	−	−	+
Spondylocladium	++		+++		++++	++	+++	++++	+++	+++	+++	−	+++	+++	−	++
Curvularia	−		++		++++	−	++	++++	+++	−	+++	−	++	−	+	++
Nigrospora	+		+		++++	−	++	(1)	++	(2)	+++	−	++	−	+	−
Control					++++		++		++		+++		+++		++	

(1) Two retests with Hormodendrum necessary to neutralize.
(2) Two retests with Helminthosporium necessary to neutralize.

TABLE I. DIRECT AND IN VIVO NEUTRALIZATION TESTS

Mold	Direct Tests				Neutralization Tests											
Patient 9 (Bruggeman)	Punch	Intradermal 1/100,000	Intradermal 1/10,000	Intradermal 1/1,000	Alternaria	Retest	Hormodendrum	Retest	Helminthosporium	Retest	Spondylocladium	Retest	Curvularia	Retest	Nigrospora	Retest
Alternaria	++++	+	++++		++++	−	++++	++++	+++	++++	++++	++++	+++	++++	+++	++++
Hormodendrum	++	+++	+++		++++	−	++++	−	+++	+	++++	−	++++	−	+++	−
Helminthosporium	+	−	++		++++	−	++++	−	+++	−	++++	−	+++	−	+++	++
Spondylocladium	++++	++	++++		++++	−	++++	+++	+++	++++	++++	−	++++	+++	+++	+++
Curvularia	+++	+	++++		++++	−	++++	−	+++	−	++++	−	+++	−	+++	+++
Nigrospora	−	−	+		++++	−	++++	−	+++	−	++++	−	++++	−	+++	−
Control					++++		+++		++		++++		+++		+	

All neutralizations carried out spontaneously.

Patient 10 (Hansen)

Alternaria	+			+++	++++	−		++++		++++		++++		++++		++++
Hormodendrum	−			−	++++	−	−									
Helminthosporium	−			−	+++	−			−							
Spondylocladium	−			−	++++	−					−					
Curvularia	−			−	++++	−							−			
Nigrospora	−			−	++++	−									−	
Control					++++											

Note: This patient obviously sensitive only to Alternaria. No other molds reacted, and sites later tested with Alternaria all reacted. Recipient refused further participation.

Patient 11 (McMinn)

Alternaria	+			++	+++	−	−	+++	+++	+++	++	+++	+++	+++	−	+++
Hormodendrum	−			−	+++	−	−	−	+++	−	+++	−	+++	−	−	−
Helminthosporium	−			++	++	−	−	+++	+++	−	+++	+++	++	+++	−	+++
Spondylocladium	+			++	+++	−	−	++	+++	−	++	−	++	+++	−	++
Curvularia	−			+	+++	−	−	++	+++	−	++	−	+	−	−	+
Nigrospora	−			−	+++	−	−	−	+++	−	++	−	++	+	+	−
Control					+++		−		++		+++		++		++	

Patient 12 (Hixon)

Alternaria	++++		+++		++++	−	+	++++	−	+++	+	++++	+	+++	+++	++
Hormodendrum	−		+		++++	−	++	−	+	++	++	−	−	++	++	+
Helminthosporium	−		−		++++	−	+	+	+	−	++	−	−	++	++	−
Spondylocladium	−		+		++++	−	+	−	++	++	++	−	−	++	++	−
Curvularia	−		−		++++	−	++	−	++	++	++	−	−	−	+++	−
Nigrospora	−		−		++++	−	+	−	−	−	++	+	−	++	++	−
Control					+++		+		−		++		−		++	

TABLE I. DIRECT AND IN VIVO NEUTRALIZATION TESTS

Mold	Direct Tests				Neutralization Tests											
	Punch	Intradermal			Alternaria	Retest	Hormodendrum	Retest	Helminthosporium	Retest	Spondylocladium	Retest	Curvularia	Retest	Nigrospora	Retest
		1/100,000	1/10,000	1/1,000												
Patient 13 (Duffy)																
Alternaria			++++ +		++++ +	−	++++	+++	+++	++++	+++	++++	+++	++++ +	−	++++ +
Hormodendrum			++++ +		++++ +	−	+++	−	+++	−	+++	−	+++	++	−	+++
Helminthosporium			++++ ++		++++ +	−	++	−	+++	−	++	−	++	+	−	++++
Spondylocladium			++++ ++		++++ +	−	+++	−	++	−	−	−	−	+++	−	+++
Curvularia			++++		++++ +	−	++	−	+++	−	++	+++	−	−	−	++++
Nigrospora			++++		++++ +	−	++	−	+++	−	++	−	−	−	−	−
Control																
C.E.A. Recipient 1 Patient 13 (Duffy)	Serum diluted 1:5 Homologous test injections were made into each site three times before cross testing. All six neutralizations were made simultaneously.															
Alternaria			++++ +		++++ +	−	++++	++++ +	+++	++	++++	++++	+++	++++ +	−	++++ +
Hormodendrum			++++ +		++++ +	−	++++	− +	+	−	+++	−	++++	++	−	++
Helminthosporium			++++ ++		++++ +	−	+++	++	+	−	−	−	−	+	−	++
Spondylocladium			++++ ++		++++ +	−	+++	++	+	−	−	−	−	−	−	+++
Curvularia			++++		++++ +	−	++	+	++	−	++++	+	+++	−	−	+
Nigrospora			++++		++++ +	−	++	−	++	−	−	−	++	−	−	−
Control																
C.E.A. Recipient 2. Serum diluted 1:5. Homologous test injections were made into each site three times before cross testing. All six neutralizations were made simultaneously. Patient 14 (Hedley)																
Alternaria			+++		++++	−	+	++++	−	++++	−	++++	−	++++	−	++++
Hormodendrum			+++		++++	−	++	−	+	++	−	+	−	++	−	−
Helminthosporium			++		++++	−	+++	−	+	−	−	−	−	−	−	−
Spondylocladium			−		++++	−	++	−	+	−	−	−	−	−	−	−
Curvularia			−		++++	−	++	−	+	−	−	−	−	−	−	−
Nigrospora			+		++++	−	−	−	−	−	−	−	−	−	−	−
Control					++++		++		−		−		−		−	
C.E.A. Serum diluted 1:5. Homologous test injections were made into each site three times before cross testing.																

IMMUNOLOGICAL STUDIES

Patients were selected who were thought to be clinically sensitive to Alternaria or other dematiaceous molds; in most instances several or all of these molds elicited positive reactions (Table I). Patients thus selected were retested with the experimental molds and discard products both by the scratch or punch method and by the intradermal technique. Sera from some of these patients were sterilized by Seitz filtration and preserved by the addition of one-hundredth volume of aqueous merthiolate 1:100, making a final concentration of 1:10,000 merthiolate.

A. In-Vivo Neutralization Studies.—Into each of six sites in a vertical row on the left aspect of the recipient's back was injected 0.08 to 0.10 c.c. of serum, and the places marked with indelible ink. A similar site to serve as a control was prepared either above the others or on the lateral aspect of the upper arm. Two days later each site was tested with 0.05 c.c. of Alternaria 1:1,000; a control test was also made in normal skin. After another twenty-four hours the first site was again tested with Alternaria, and if all reagin had been exhausted by the first test, indicated by a negative reaction, the remaining sites were tested in order with the other five molds. The control site higher on the back or on the arm was then tested with Alternaria to verify the persistence of reagin. In one or two instances retest of all the sites with the homologous mold was necessary to effect complete neutralization before proceeding with the cross testing after an additional twenty-four hours. After completion of the tests another row of sites was prepared to the right of the first for similar exhaustion by Hormodendrum. In like manner each of the molds in turn was studied (Table I). All tests both for the initial exhaustions as well as for the cross reactions were accompanied by control tests in normal skin, according to the Prausnitz-Kustner technique.

B. In-Vitro Neutralization.—The neutralizing mixtures of allergen and sensitive serum were prepared by placing 0.30 c.c. each of 1:1,000 mold extract, serum, and normal saline into sterile test tubes which, after thorough shaking, were allowed to stand in the refrigerator over night. Into each of six sites arranged in a vertical row on the left side of the recipient's back was injected intradermally 0.10 c.c. of this mixture. At the same time control sites A and B were prepared on the outer aspect of the upper arm as follows: Into site A was injected 0.10 c.c. of a 1:3 dilution of serum in normal saline (the serum in control A therefore was in the same dilution as in the serum-antigen-saline mixtures). Into site B was injected 0.10 c.c. of undiluted serum. After forty-eight hours the sites on the back were tested with 0.05 c.c. of each of the respective mold extracts 1:10,000, and the control sites A and B were tested with the homologous mold. Within a few minutes if no reactions occurred, or after five or

six hours to allow reactions to subside, the sites were again tested with the same molds in 1:1,000 dilution. In like manner neutralization with each of the molds in succession was performed. The results are recorded in Table II. In both the *in-vivo* and *in-vitro* experiments, some variations were made from the technique as given above; such modifications are noted in the tables.

RESULTS

At the outset we wish to stress the fact that these studies, involving several mold-sensitive allergic patients, can only be expected to reveal differences in sensitization to the various molds depending on the reaginic activity of the individual patients and their sera. Therefore, any conclusions must be interpreted with this in mind and cannot be construed as confirming otherwise defined botanical relationships between the molds themselves.

In most of the sera studied in experiments A and B, Alternaria exhausted the reagins for all other molds. However, Alternaria failed to exhaust reagins for Helminthosporium and Spondylocladium in the *in-vivo* neutralization, and for Helminthosporium in the *in-vitro* experiment with serum 1; for Helminthosporium and Curvularia in both experiments with serum 3, and for Spondylocladium in the *in-vivo* studies with sera 8 and 9. Conversely, in serum 1, Spondylocladium, Curvularia and Helminthosporium appreciably diminished, but did not entirely block the reaction on cross testing with Alternaria in both experiments. In serum 3 Curvularia completely exhausted reagins for Alternaria, while Helminthosporium and Spondylocladium greatly diminished the reaction in the *in-vivo* experiment; all three apparently diminished the reaction on cross testing with Alternaria in the *in-vitro* study. In sera 8 and 9 furthermore, Spondylocladium exhausted reagins for all molds except Alternaria, whereas no Heterologous mold including Alternaria exhausted reagins against Spondylocladium. In all the tests Hormodendrum neutralized Nigrospora reagins, but the reverse was not true in five instances.

In general, the antibody exhausting power of any particular mold seemed unpredictable, except for the fact that those molds giving large transfer reactions on the initial testing in the *in-vivo* neutralizations seemed to neutralize more reagins for other molds, and they in turn seemed more difficult to be neutralized. Significant differences in reactivity seemed to depend more on the reaginic variations of the sera than on the mold extracts. All the sera varied in reagin content. Serum 10 was exceptional in that it contained reagins to only one mold of the dematiaceous group (Alternaria). In several of the sera reagins were lacking or of low titer for one or more molds. In most instances reagins were present for all the molds.

It is obvious that the *in-vivo* and *in-vitro* tests gave comparable results.

Actually, the *in-vitro* procedure is simpler and probably is subject to less error than is the *in-vivo* technique because in the test tube, mixture of

TABLE II. IN-VITRO NEUTRALIZATION TESTS

Serum—Saline—Antigen:	Alternaria		Hormodendrum		Helminthosporium		Spondylocladium		Curvularia		Nigrospora	
Cross testing with:	1/10,000	1/1,000	1/10,000	1/1,000	1/10,000	1/1,000	1/10,000	1/1,000	1/10,000	1/1,000	1/10,000	1/1,000
Patient 1 (Davies)												
Alternaria	−	−	+++	−	+	−	+	−	++	−	+++	−
Hormodendrum	−	−	−	−	−	−	−	−	−	−	+	−
Helminthosporium	++	−	++++	−	−	−	+	−	+	−	+++	−
Spondylocladium	−	−	++	−	−	−	−	−	−	−	++	−
Curvularia	−	−	++	−	−	−	−	−	−	−	+	−
Nigrospora	−	−	−	−	−	−	−	−	−	−	−	−
Control A 1/3 serum	+	−	+	+++	+++	−	+++	−	++	−	−	−
Control B serum undiluted	+++	−	++	+++	+++	−	+++	−	+++	−	+	−
Patient 2 (Rowles)												
Alternaria	−	−	++++	−	++++	−	++++	−	++++	−	+++	−
Hormodendrum	−	−	−	−	−	−	−	−	−	−	−	−
Helminthosporium	−	−	−	−	−	−	−	−	−	−	−	−
Spondylocladium	−	−	−	−	−	−	−	−	−	−	−	−
Curvularia	−	−	−	−	−	−	−	−	−	−	−	−
Nigrospora	−	−	−	−	−	−	−	−	−	−	−	−
Control A 1/3 serum	++++	−	++	++	+++	−	−	−	−	−	++	−
Control B serum undiluted	+++	−	++	+++	+++	−	+++	−	+	−	+++	−
Patient 3 (Keene)												
Alternaria	−	−	++++	+	+	−	++	−	+	−	+++	−
Hormodendrum	−	−	−	−	−	−	−	−	−	−	−	−
Helminthosporium	++	−	+++	−	−	−	−	−	−	−	+++	−
Spondylocladium	+++	−	++++	−	++	+	−	−	−	−	++++	−
Curvularia	++	+	+++	+	+++	+	++	−	−	−	+++	−
Nigrospora	−	−	−	−	++	++	+++	−	−	−	−	−
Control A 1/3 serum	+++		+	+	++	+	+++		+++		+	
Control B serum undiluted	+++		++	+	+++	++	+++		+++		++	

TABLE II. IN-VITRO NEUTRALIZATION TESTS

Serum—Saline—Antigen:	Alternaria		Hormodendrum		Helminthosporium		Spondylocladium		Curvularia		Nigrospora	
Cross testing with:	1/10,000	1/1,000	1/10,000	1/1,000	1/10,000	1/1,000	1/10,000	1/1,000	1/10,000	1/ 1,000	1/10,000	1/1,000
Patient 4 (Hornbuckle)												
Alternaria	–	–	++++	–	+++	–	+++	–	+	–	++	–
Hormodendrum	–	–	–	–	+	–	+	–	–	–	–	+
Helminthosporium	–	–	++	–	–	–	–	–	–	–	+	–
Spondylocladium	–	–	+	–	++	+	–	–	–	–	+	–
Curvularia	–	–	+	–	++	++	++	–	–	–	–	–
Nigrospora	–	–	–	–	++	+++	++	–	++	–	–	–
Control A 1/3 serum	++		+	++	++	–	–	–	–	–	+	
Control B serum undiluted	+++		+	++	++	–	++	–	++	–	++	
Patient 13 (Duffy)												
Alternaria		–		+++		+++		+++		+++		+++
Hormodendrum		–		–		–		–		–		–
Helminthosporium		–		–		–		–		–		–
Spondylocladium		–		–		–		–		–		–
Curvularia		–		–		–		–		–		–
Nigrospora		–		–		–		–		–		–
Control A 1/3 serum												
Control B serum undiluted												

C.E.A.

Neutralizing mixtures: 0.5 cc serum 1:2, 0.5 cc saline, 0.5 cc 1/1,000 mold extracts. All sites tested with homologous antigens and found negative before cross testing.

TABLE III. TESTS WITH EXPERIMENTAL EXTRACTS AND DISCARD PRODUCTS

Mold	Patient 1 (Davies)		Patient 2 (Rowles)				Patient 3 (Keene)		Patient 4 (Hornbuckle)		Patient 5 (Bastian)		Patient 6 (Hicks)	
	Punch	Intradermal	Punch	Intradermal			Punch	Intradermal	Punch	Intradermal	Punch	Intradermal	Punch	Intradermal
		1/1,000		1/100,000	1/10,000	1/1,000		1/10,000		1/10,000		1/10,000		1/10,000
Alternaria	+	++++	+	++	+++		++	++	++	+++	+++	+++	++	++++
Discard	+	−	−	−	+		−	+	−	−	−	+	−	−
Hormodendrum	+	++++	+	+	+++		++	+	−	−	+	++	−	+
Discard	−	−	−	−	−		+	−	−	−	−	−	+	−
Helminthosporium	+	+++	−	+	++		++	++	+++	++	+	+	+	+
Discard	−	+	−	−	−		−	+	−	−	−	−	−	+
Spondylocladium	++	++++	+	+	++		+++	++++	++	+	+	+	−	−
Discard	−	−	−	−	−		+	++	−	−	−	+	−	−
Curvularia	++	++++	++	+	++		−	++	−	++	++	++	−	−
Nigrospora	−	−	−	−	−	+	+	+	−	−	−	−	−	+

Mold	Patient 7 (Crawford)		Patient 8 (Gordon)		Patient 9 (Bruggeman)			Patient 10 (Hansen)		Patient 11 (McMinn)		Patient 12 (Hixon)	
	Punch	Intradermal	Punch	Intradermal	Punch	Intradermal		Punch	Intradermal	Punch	Intradermal	Punch	Intradermal
		1/1,000		1/10,000		1/100,000	1/10,000		1/1,000		1/1,000		1/10,000
Alternaria	+	+++	+	+++	++++	+	++++	+	+++	+	++	++++	+++
Discard	−	+	−	−	+	−	++	−	+	−	+	+	+
Hormodendrum	+	−	−	+	++	+++	+++	−	−	−	−	−	+
Discard	−	−	−	−	−	−	+	−	−	−	−	−	−
Helminthosporium	+	++	−	++	+	−	++	−	−	+	++	−	−
Discard	−	−	−	−	−	−	−	−	−	+	+	−	−
Spondylocladium	−	++	++	+++	++++	++	++++	−	−	+	++	−	+
Discard	−	−	−	+	++	+	++	−	−	−	+	−	−
Curvularia	−	−	−	++	+++	+	++++	−	−	−	+	−	−
Nigrospora	−	−	+	+	−	−	+	−	−	−	−	−	−

TABLE III. TESTS WITH EXPERIMENTAL EXTRACTS AND DISCARD PRODUCTS

Mold	Patient 13 (Duffy)	Patient 14 (Hedley)	Patient 15 ("III")	Patient 16 (Gordon)		Patient 17 (Franchot)		Patient 18 (Petty)	
	Intradermal	Intradermal	Intradermal	Punch	Intradermal	Punch	Intradermal	Punch	Intradermal
	1/10,000	1/10,000	1/1,000		1/1,000		1/10,000		1/1,000
Alternaria	+++++	+++	++	+	++	++	+++	−	++
Discard	+++	++	+	−	+	−	−	−	−
Hormodendrum	+++++	+++	+++	−	+	++	++++	−	+
Discard	+++	+++	−	−	−	−	−	−	−
Helminthosporium	+++++	++	+++	−	−	+	++	+	+
Discard	+++	−	−	−	−	−	−	−	−
Spondylocladium	++++++	−	+++	−	−	++	++	+	+
Discard	++++	+++	+	−	−	−	+	+	−
Curvularia	++++	−	−	−	−	++++	++	−	+++
Nigrospora	++++	+	−	−	+	−	+	−	+

Mold	Patient 19 (Anderson)		Patient 20 (J.T.W.)			Patient 21 (Darr)		Patient 22 (Stromberg)	Patient 23 (Randel)	
	Punch	Intradermal	Intradermal			Punch	Intradermal	Intradermal	Punch	Intradermal
		1/10,000	1/100,000	1/10,000	1/1,000		1/1,000	1/10,000		1/1,000
Alternaria	++++	+++	++++	−		−	+	+++++	+	++++
Discard	−	−	−		−	−	−	−	−	+
Hormodendrum	−	+	++	−		+	+++	+++	−	−
Discard	−	−	−	+		−	−	−	−	−
Helminthosporium	++	+	++	−		+	+++	++	−	++
Discard	−	−	−		−	−	−	+++	−	−
Spondylocladium	+	−	+++	−		+	+++	+	−	++
Discard	−	−	−	−	−	−	−	+	−	+
Curvularia	+	−	++	−		−	+	−	−	+
Nigrospora	−	−	−	−	−	−	−	−	−	−

antigen and antibody should be more thorough and complete. Unfortunately, we were unable to perform *in-vitro* neutralization on all the sera studied.

SKIN TESTS WITH EXTRACTS AND DISCARD PRODUCTS

The mold extracts and discard products were used in concentrated strength (1:50) for punch (scratch) testing, and in dilutions ranging from 1:100,000 to 1:1,000 intradermally. The tests were made either with arbitrary dilutions intradermally (C.E.A., E.D.S.) or by both the punch (scratch) and intradermal techniques, with the solutions for the intradermal tests being selected on the basis of the preliminary punch (scratch) reactions (P.T.P., H.E.P.). The results of these tests are shown in Table III.

Obviously the discard products contain appreciable amounts of antigen, indicating that not all the skin reactive fractions were retained in the extracts (Patients 13 and 14). However, most tests indicated that the discard products contained relatively much less antigen than the extracts. This is not clearly apparent in Patients 13 and 14 with the 1:10,000 intradermal tests; these patients obviously were very highly sensitive to dematiaceous molds, and probably dilutions greater than 1:10,000 would be required to show differences.

One of us (E.A.B.) injected intradermally 0.10 c.c. of 1:1,000 experimental Alternaria extract into an individual known to be Alternaria sensitive. In three minutes he was wheezing and his nasal passages were blocked in spite of a tourniquet applied as soon as the reaction was detected. Three days later the forearm tested still showed a reaction, the swollen area measuring 1.5 inches, the surface of the arm from the wrist to the elbow being indurated. The discard product of Alternaria, 0.10 c.c. of 1:1,000, gave a negative skin reaction.

DISCUSSION

These experiments suggest that extracts of molds of the dematiaceous group prepared by Technique 33 possess specific allergenic properties. We believe furthermore that the technique is adequate with the other molds of the group as has been pointed out previously for Alternaria. We know that some allergen is lost in the process, but we feel very definitely that this is more than compensated by the increased potency and specificity of the extracts.

In unpublished experiments several years ago, one of us (H.E.P.) was able to neutralize reagins to other dematiaceous molds with Alternaria by the exhaustion of passively sensitized sites, using, however, extracts prepared by our old routine technique.[2] Furthermore, diagnostic and therapeutic results were no better with a mixture of all the dematiaceous molds than with Alternaria alone. Following these observations, reactions with any of the dematiaceous molds were regarded more from the standpoint of substantiating the group sensitization, as typified by Alternaria, than

of indicating sensitization to the particular reacting molds. This interpretation doubtless was influenced further by the fact that Alternaria usually reacted when *any* dematiaceous species did; failure of Alternaria to react often cast doubt on the reliability of the positive tests from others of the group. The use of Alternaria as a *group antigen* therapeutically, therefore, seemed justified.

In the light of the findings presented herewith, the rationale of using Alternaria therapeutically for all reactions to molds of the dematiaceous group must be questioned. It cannot be doubted that Alternaria would probably protect eleven of the fifteen patients reported in Experiment A, but Alternaria alone would be inadequate in Patients 1, 3, 8 and 9 upon clinical exposure to those molds not neutralized. This failure at protection with Alternaria was observed in Patient 1, whereupon re-evaluation of skin test results led to a study of her serum in Experiments A and B.

CONCLUSION

The dematiaceous molds herein studied seem to contain group antigens as well as generic or possibly species antigens. Sensitization to these molds, however, must be evaluated in the light of the actual reagins demonstrable in any given patient; such reagin distribution is variable. Ordinarily it would seem that Alternaria should protect against other molds of the group, but occasionally other molds may assume dominant importance immunologically. If generic or species reagins exist to these other molds, they would require consideration from a therapeutic standpoint.

We hope that with the adequate extracts now available further immunological studies may be made to verify or revise our conclusions, which at this time seem justified.

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MOLD FUNGI IN THE ETIOLOGY OF RESPIRATORY ALLERGIC DISEASES

XIII. The Use of a Concentrated Extract in the Treatment of Mold-Sensitive Patients

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SINCE October, 1947, we have treated approximately 200 patients sensitive to mold with concentrated Alternaria extract (Series 33) supplied by Dr. Prince. Prior to this extracts obtained from commercial sources were used for diagnosis and treatment.

Comparative scratch tests were used to assay the potency of the two brands. It was found that Alternaria 33 in a dilution of 1:200 (concentrated, labeled 1:50) gave comparable skin reactions to concentrated commercial extract (labeled 1:10). Hence we have continued to used the 1:200 dilution as the maximum concentration and have made dilutions in multiples of 10 (1:2000, et cetera). In the average case we begin treatment with a 1:200,000 dilution and rarely exceed a 1:2000 dilution in any case. That the extract is very potent is evidenced by constitutional reactions occurring when the patient's tolerance is exceeded by increase in dosage.

From our observations, we are certain this extract is diagnostically specific for Alternaria. It gives clear-cut positive reactions by scratch technique quite comparable to those given by strong pollen extracts. A large series of controls confirmed its specificity. Furthermore, the potency of different lots of extract remained quite constant, so that no difficulties were encountered in changing to a new batch of extract. This was in distinct contrast to our experience with commercial extracts, where a great variance in potency was observed. Indeed, an occasional lot would fail to exhibit any antigenicity as judged by skin test response. The uniformity of Alternaria 33 thus eliminates the difficulties usually experienced when a new batch of extract is received.

Statistical evaluation of our results is impossible at this time because of several factors. Of the 200 cases, only fifteen reacted to Alternaria alone. Criterion for diagnosis was a good clinical history correlating with positive skin tests. More than half of the group also reacted by skin test to Hormodendrum and Helminthosporium. Only recently have concentrated extracts of these been available, and we had to depend on unreliable commercial extracts. The majority of patients were mold and pollen sensitive, and it is difficult to assess the therapeutic value of the mold extracts in these combined cases. Furthermore, it has always been our practice to use no extract for diagnosis or treatment until it is evaluated on known sensitive patients as well as a control negative

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group. Hence, the advantages of the unformity of the concentrate No. 33 were not apparent in our results from treatment.

On the basis of clinical experience and judgment, we believe the results from treatment with concentrate No. 33 were distinctly better than when commercial extract was used. This was more apparent in the fifteen cases of pure Alternaria sensitivity. We now have as much confidence in the therapeutic value of these concentrated extracts as in our own pollen extracts, where previously we were most uncertain about the therapeutic worth of commercial extracts.

Hence, we feel that we have been supplied with a uniformly potent Alternaria extract, free of irritative materials, that gives excellent results in the treatment of Alternaria-sensitive patients. It is so concentrated that we now require only one-fourth the amount of undiluted extract as when we relied on commercial sources. These factors, in addition to its specificity, have greatly simplified diagnosis and clinical management of the Alternaria-sensitive patient.

FIRST INTERNATIONAL CONGRESS ON ALLERGY

All those from North America and South America who plan to attend the First International Congress on Allergy at Zurich, Switzerland, September 23 through 29, 1951, should write to the Chairman of the Executive Committee of the International Association of Allergists, 424 La Salle Medical Building, Minneapolis 2, Minnesota, stating their preference for travel, whether by boat or plane, and how long they plan on being in Europe. The American Express Company has been appointed as the official travel agency for the Congress. The average time for the trip has been planned for two months, although shorter itineraries can be arranged to suit the individual. It is obvious that all arrangements made by an internationally known travel agency, the American Express Company with offices in all countries, will result in the highest type of service. If you prefer to make arrangements through your local travel agency, it will be satisfactory; the local agency will handle your trip through the American Express Company without additional cost to you. It is important that we get an approximate number of those who will attend from America and countries outside Europe. When planning your itinerary, it is important to know that it is almost impossible to go by boat and return by plane, or vice versa, because competition is so great that transportation lines refuse to issue a one-way ticket. You will soon be receiving a prospectus containing detailed information about the Congress. A representative of the American Express Company will be at a booth in the New Hotel Jefferson, St. Louis, during the annual meeting of the College.

PROCEDURE FOR DETERMINATION OF AEROSOL DELIVERY AND STABILITY DURING NEBULIZATION

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THE collection of aerosols of heterogeneous particle size of about 3 micra and below is complicated by the fact that these particles are too small to be trapped by liquids at room temperature. It became necessary during a recent study of the inhalation of aerosols of vitamin C to ascertain if the sodium ascorbate in the nebulizer was rapidly destroyed by the atomizing stream of oxygen which was used to generate the aerosol.[2] The residue of the sodium ascorbate in the nebulizer was readily obtained and titrated. There remained, however, the more difficult problem of collecting and titrating an aerosol of a substance presumably rapidly decomposed during nebulization by oxygen. Collection of the main fraction of the nebulized material by the technique herein described makes possible the establishment of a balance sheet of sodium ascorbate which was broken down incidental to the production and collection of the aerosol. In general, the dosage of labile aerosols may thus readily be ascertained.

Although there are estimates of the quantity of therapeutically active substances which actually are deposited in the lung during nebulization therapy, most of these disregard deposits in the upper respiratory tract. Studies attempting to establish minimum values for lung deposition of aerosols of various types are now in progress. Without the determination of aerosol stability in questionable cases, the procedure is made difficult.

METHODS

The centrifugal coil of Abramson and Demerec[3] was adapted by inverting the coil and changing the dimensions as follows: the length of the coil (Fig. 1) was 40 cm.; the radius of each coil was 1.25 cm.; the internal diameter of the tubing was 4 mm. The total length of the glass comprising the coil should be at least 3 meters. The actual size can readily be visualized from Figure 1 where a coil is connected with a DeVilbiss No. 40 nebulizer. It is most important that the coil be connected with a glass connection of the same diameter as the nebulizer itself. If this is not done, the large majority of particles are baffled out by the connection and the output of the nebulizer is diminished considerably by the intervening baffle.

With the present design, nebulization must be accomplished with a rubber stopper in the air vent in the side of the nebulizer. A leak of

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The phenolsulfonphthalein was especially prepared by Hynson, Westcott and Dunning.

The sodium ascorbate was kindly supplied by the Van Patten Pharmaceutical Co.

aerosol otherwise occurs because of the back pressure of the liquid in the coil as well as the resistance to airflow occasioned by the small diameter of the coil tubing. The collecting vessel illustrated in the figure was especially constructed to just fit the coil. The volume of liquid placed

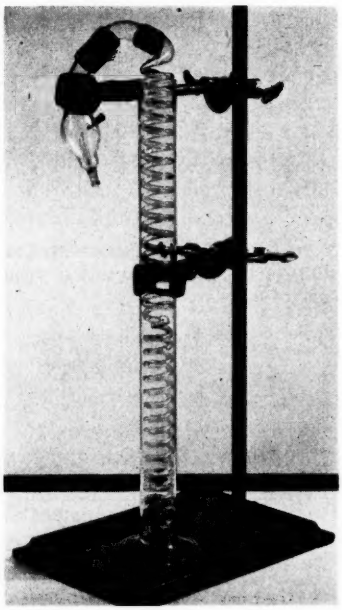

Fig. 1. Centrifugal coil for aerosol collection.

in the collecting vessel was 50 c.c. Even with this volume of liquid and numerous coils of small radii, not all of the aerosol was ever collected. A very faint mist was always seen emerging out of the liquid in the collecting vessel. This light mist which arises from the surface of the liquid is, however, quite negligible as far as our experimental results obtain. This is obvious not only from our experimental data, but is also evident from the geometry of the particle size distribution. The mass of any particle is proportional to the cube of the radius of the particle. The dose in a particle 0.1μ in radius is one thousandth the dose in a particle 1.0μ in radius. It is evident, then, that with the very small particles which escape the action of the coils, the weight loss is small.

The principle of the centrifugal coil is readily explained. The force F, acting on a particle moving in a circular path in a current of air is given by the equation:

$$F = M\ (V^2/r)$$

where M is the mass of the particle, V is the particle velocity, and r is the radius of curvature of the path. If the particle takes a circular path,

TABLE I. EFFECT OF INCREASING VOLUME VELOCITY OF AIR ON NEBULIZER DELIVERY

Initial Volume of Liquid: 2 c.c.

Time: 10 minutes

Corrected Airflow (Liters/min.) A	Initial PSP in Nebulizer (mg.) 1	PSP Condensed by Coil (mg.) 2	Residual PSP in Nebulizer (mg.) 3	PSP Delivered by Nebulizer (mg.) 4	Per Cent Delivery 5	Per Cent Loss of Delivered PSP 6	Mg. PSP Delivered Per Liter Airflow Per Min. 7
4.5	41.8	1.6	40.0	1.8	4.3	+9.5	0.040
5.2	41.8	2.4	39.5	2.3	5.5	—0.0	0.044
6.2	41.8	8.2	33.3	8.5	20.3	+4.1	0.138
6.9	41.8	11.7	30.5	11.3	27.0	—3.5	0.164
8.0	41.8	13.1	28.1	13.7	32.8	+4.4	0.172
9.4	41.8	16.3	26.0	15.8	37.8	—3.2	0.168
11.5	41.8	18.7	23.7	18.1	43.3	—3.3	0.157

TABLE II. EFFECT OF INCREASING CONCENTRATION OF SOLUTE ON NEBULIZER DELIVERY AT LOW VOLUME VELOCITIES OF AIR

Corrected Airflow (liters/min.) A	Initial PSP in Nebulizer (mg.) 1	PSP Condensed by Coil (mg.) 2	Residual PSP in Nebulizer (mg.) 3	PSP Delivered by Nebulizer (1-3) 4	Per Cent Delivery (4/1) 5	Mg PSP Delivered per Liter Airflow Per Minute (4/A) 6
4.0	4.2	0.6	3.6	0.6	14.3	0.016
4.0	19.0	2.6	16.0	3.0	15.8	0.072
4.0	22.0	2.6	18.7	3.3	15.0	0.080
4.0	36.6	4.9	31.4	5.2	14.2	0.124

TABLE III. EFFECT OF INCREASING GLYCEROL CONCENTRATION OF DELIVERY BY NEBULIZER

2 c.c. P. S. P. (11.2 mg.) at 5.7 L/min. for Ten Minutes

Per Cent Glycerol	PSP Condensed by Coil (mg.)	Residual PSP in Nebulizer (mg.)	PSP Delivered by Nebulizer (mg.)	Per Cent Delivery
0	2.9	8.1	3.1	26.9
10	2.9	8.2	3.0	26.9
15	2.8	8.2	3.0	25.0
20	2.6	8.5	2.7	24.1
25	2.3	8.2	3.0	23.2

therefore, with the velocity being held constant, the force acting on the particle is the greater, the smaller the radius of curvature of the path. This notion is not at all intuitive, as is clarified by the following examples: If two men stand at different points on the radius of a merry-go-round, it is evident that the one standing further from the axis of rotation will tend to be thrown off more than the one nearest the axis. Thus, the greater the linear velocity the greater the centrifugal force. This case is not analogous to the centrifugal fractionator since the linear velocity is kept constant. If, however, another example is used, the way in which the coil operates on aerosols is clarified. A train going around a track at a given velocity, say of 60 miles an hour, will not tend to be thrown off the track as much

if the track has a great radius of curvature as it would if the track has a small radius of curvature. In other words, the particles in the centrifugal fractionator act in much the same way as a train going around tracks of different radii of curvature with constant linear velocity. Other factors, such as the distances separating the coils of the fractionator, also play a role, but the treatment of these are beyond the scope of this paper.

The operation of the centrifugal coil, as adapted to the study of nebulizer delivery and aerosol stability, throws light on the behavior of the nebulizer under varied conditions. Although the construction of and the nature of the air jet, liquid feed and housing of the nebulizer lead to a certain degree of variation between nebulizers of the same construction, the data is of great interest in that the generalities derived from the data are qualitatively correct for all nebulizers of the type utilized.

Stock phenolsulfonphthalein in sterile ampules and vaccine bottles containing respectively 18 and 500 milligrams per c.c. of the dyestuff was diluted as indicated. Concentrations were checked against standards colorimetrically by the method described below. Solutions for volumetric determinations of sodium ascorbate were prepared according to directions in the United States Pharmacopeia No. XII.

Phenolsulfonphthalein determinations were made with the Klett-Summerson photoelectric colorimeter (Filter: 54 K-S), using standards prepared from the 6 mg. commercial ampules. The dye solutions were alkalinized with 5 c.c. per liter of 5 per cent potassium hydroxide. The limit of error was approximately 5 per cent.

The same DeVilbiss No. 40 nebulizer was used in any single series of experiments given in the tables. Different nebulizers were used for different series of experiments. The data from table to table are therefore qualitatively, but not quantitatively, interchangeable.

The airflow was corrected by determining the rate of airflow from the mouth of the nebulizer using a Precision Wet Gas Test Meter manufactured by the Precision Scientific Company. Correction was thereby automatically made for the increased resistance to flow velocity incurred by the decreased tube diameter of the centrifugal coil.

Sufficient solution was used so that the jets produced the same quantity of aerosol per unit time at the beginning and at the end of the experiment. The quantity of phenolsulfonphthalein given in Column 1 of Tables I, II and III was dissolved in 2 c.c. of normal saline.

Experiments lasted for ten minutes with the gas air pump or an oxygen cylinder. The stability experiment with sodium ascorbate in Table IV lasted fourteen minutes with an oxygen flow of 5 liters per minute.

The centrifugal apparatus is depicted in Figure 1. The test solution was added to the nebulizer, the gas turned on and permitted to run for the prescribed time with the vent closed. The equipment train was then broken at the rubber-glass connection closest to the nebulizer. This point

separates the nebulizer residue from the coil condensate. The coil was then washed three times with distilled water and the washings diluted to one liter after the addition of 5 c.c. of 5 per cent potassium hydroxide. This is the coil condensate of Column 2, Tables I and II. Care must be

TABLE IV. FRACTIONAL CONDENSATION OF APPROXIMATELY 20 PER CENT SODIUM ASCORBATE

(1 c.c.=18.9 c.c. N/10 Iodine)

Time Nebulized	N/10 Iodine
2 min.	0.56
4 min.	0.56
6 min.	0.62
8 min.	0.59
10 min.	0.62
12 min.	0.48
14 min.	0.61

Nebulized	4.04 c.c.	of Sodium Ascorbate recovered from coil.
Nebulizer residue	13.94 c.c.	
TOTAL	17.98 c.c.	or a loss equivalent to about 1 c.c. of N/10 Iodine.

taken to collect all of the dyestuff at the various rubber-glass connections, since a small loss may produce a larger error in this part of the procedure. The nebulizer was then washed so that no color resulted upon the addition of alkaline wash water. These washings were diluted to 1 liter after the addition of 5 c.c. of 5 per cent potassium hydroxide. This represents the nebulizer residue of Column 3, Tables I and II. Determinations on the liter washings are run with aliquots, so diluted as to bring the concentrations within the range of the standards employed.

The experiments with sodium ascorbate, Table IV, were performed similarly except that the coil condensate was determined separately at various time intervals noted. The nebulizer residue was estimated at the conclusion of the experiment.

RESULTS

Column 6 of Tables I and II show a spread of the per cent loss of Initial PSP from — 1.0 per cent to + 3.4 per cent. This is well within the limits of experimental error. The effect of volume velocity on collection efficiency is likewise negligible since the per cent loss goes from + 0.4 per cent at 4.5 liters per minutes to — 1.4 per cent at 11.5 liters per minute. This negligible loss results despite the fact that a faint mist of aerosol is always seen leaving the coil.

Effect of Increasing Volume Velocity on Nebulizer Delivery.—Table I indicates that the per cent delivery rises from 4.3 per cent at 4.5 liters per minute to 43.3 per cent delivery at 11.5 liters per minute, with condi-

tions otherwise being constant. The efficiency of nebulization does not follow the same quantitative trend, since the output expressed in milligrams of PSP delivered per liter airflow per minute (Column 7) approaches a maximum at about 7 liters per minute. In this experiment it decreased slightly with the highest air velocity. However, this decrease is not marked. With this nebulizer the efficiency increases between 5.2 and 6.2 liters per minute. Very effective use of the nebulizer is at about 10 liters per minute. (Nasal tips are needed.) Various nebulizers differ in their points of maximum efficiency.

Effect of Increasing Solute Concentration on Nebulizer Delivery.—With constant velocity of airflow, increasing the PSP concentration from 4.2 mg. to 35.6 mg. showed no influence on the per cent delivered. (Table II.) However, the total PSP delivered by the nebulizer (Column 4) increased from 0.6 mg. with 4.2 mg. per c.c. initially to 5.2 mg. delivery with 36.6 mg. per c.c. initially. The milligrams of PSP delivered per liter per minute likewise rose from 0.016 to 0.124 mg. per liter per minute.

Effect of Increasing Glycerol Concentration on Nebulizer Delivery.—It is common clinical practice to use glycerol as a vehicle in nebulization therapy. The effect of glycerol is illustrated in Table III. With increasing concentrations of glycerol, the per cent delivery hardly changes, whereas the coefficient of viscosity approximately doubles at a concentration of 25 per cent glycerol.

Sodium Ascorbate Stability during Nebulization with Oxygen.—At the beginning of the experiments with vitamin C the authors employed ascorbic acid. The solutions were found to be irritating to patients. This was due to the low pH. Sodium ascorbate was substituted and found not to be irritating even in concentrations up to 20 per cent. The coil experiments were subsequently carried out with sodium ascorbate. The data appears in Table IV. It is noted that after fourteen minutes, 21.3 per cent of the original sodium ascorbate has been collected by the centrifugal coil with a loss of approximately 5 per cent, or about 0.05 c.c., of the original 1 c.c. solution of sodium ascorbate placed in the nebulizer.

The results dealing with delivery of the dye are directly applicable to clinical usage. In order to increase dosage of nebulized medication and hence increase the therapeutic efficiency and shorten the time of therapy the following points are of importance:

1. Increase velocity airflow. A practical level is 10 liters per minute, with nasal tips similar to the DeVilbiss No. 640.

2. Increase concentration of medication.

In increasing the velocity of airflow to 10 liters per minute the oral method of administration may be irritating. It was found that the De-

Vilbiss nasal tips which permit administration of aerosols, resulted in lessened or no irritation at the higher velocities of airflow and concentration. A shortened time for therapeutic aerosol delivery is, of course, obtained. This procedure makes certain that the aerosol is delivered exactly at inspiration because the mouth is closed and air reaches the patient only through the nebulizer. In this way we have been administering solutions containing approximately 1,000,000 units of crystalline penicillin G per c.c. The patient is much more comfortable and co-operative with this shortened procedure. It has not been decided whether open or closed vents are desirable in therapy.

A series of subjects have received 10 and 5 per cent PSP for fifteen minutes at 10 liters per minute, with nasal tips. Utilizing the principles put forth in this paper, PSP is being tested, at present, as a chemical indicator in experiments in man. It may be stated that this method shows promise as a means of studying the behavior of antibiotic aerosols in the lungs, bronchi, and systemically, and also as a possible lung function test. A full report of these experiments will appear in a subsequent paper now in preparation.

The data of Table IV shows rather surprisingly that during the nebulization of this high concentration of sodium ascorbate, a comparatively small amount of decomposition of the sodium ascorbate occurred in the presence of oxygen. Dilute solutions of sodium ascorbate showed the expected rapid decomposition of vitamin C which can be readily followed by the same procedure. Diverse properties of medical significance have been ascribed to vitamin C. Among these are anti-viral activities, enzyme inactivation, formation of collagen in connective tissue, and acceleration of fibrosis in the therapy of tuberculosis. Our procedure shows that it is feasible to employ vitamin C as an aerosol for topical therapy in suppurative and other infectious pulmonary diseases, provided that sufficiently high concentrations are used.

Preliminary experiments indicate the 15 per cent sodium ascorbate may be inhaled for fifteen minutes as an aerosol without irritation by patients with severe asthma. A 10 per cent solution can be given six times daily without irritation. In all likelihood, higher concentrations could probably be used.

SUMMARY

1. A centrifugal coil which efficiently condenses aerosols produced by commonly used nebulizers is described.

2. The effects of volume velocity, initial concentration, and viscosity of the liquid in the nebulizer, on delivery by the nebulizer, are discussed on the basis of quantitative data.

3. It is shown by this procedure that sodium ascorbate aerosol, nebulized

(Continued on Page 638)

PENICILLIN SENSITIVITY

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WITH the widespread use of penicillin in otolaryngology, a significant number of patients will manifest allergic reactions to this drug, and the problem of management of such reactions is of practical importance. Just as in the case of the sulfonamides, there is ample evidence that penicillin is being used indiscriminately. We have encountered a number of instances in which it was used unnecessarily in the treatment of the common cold and was followed by the typical serum-disease-like reaction, with generalized urticaria and angioneurotic edema. In many cases of infection encountered in otolaryngology, the severity is not sufficiently marked to indicate the use of penicillin.

The most common type of reaction manifested to penicillin simulates serum disease. It is characterized by the same incubation period of seven to ten days, followed by urticaria, angioneurotic edema, itching, fever, and joint pains. In some instances, the symptoms may be mild and transitory, and they may be readily controlled by the administration of the antihistaminic drugs. On the other hand, very severe reactions may occur which are not controlled by the ordinary methods of treatment.

Since the advent of the therapeutic use of penicillin, the literature has become replete with articles dealing with the occurrence of untoward reactions. Most of the pertinent information has been recently reviewed and summarized in a few important presentations which will be outlined below. For further details, one may consult the papers of Peck and his associates,[2] Prince and Etter,[3] and the review of the literature by Epstein and Macaulay.[1]

According to Peck, there are two distinct types of reaction to penicillin: (1) the serum-sickness-like urticarial type which is an induced sensitivity, and (2) the eczematoid-trichophytid-like type which may be based upon a previous sensitivity produced by a fungous infection. The so-called "spontaneous" penicillin-sensitive cases belong to this latter group. Exfoliative dermatitis following penicillin administration appears to be of rare occurrence and of the mild type.

Although reactions may occur to either the commercial preparations or the pure crystalline types, they appear to be more common to the former. On the other hand, it has been shown that reactions may occur from the impurities in commercial preparations and not the penicillin itself.

Besides the parenteral route, other routes of administration must be considered. There is considerable difference in the sensitizing potential where penicillin is applied to different areas of the skin and mucous membranes. The face and mouth particularly appear to be more sus-

ceptible. Penicillin aerosol, used for respiratory infections, has resulted in stomatitis, nasal irritation, and dermatitis around the nose and mouth in about 5 per cent of the cases. Stomatitis from oral administration occurs in about 14 per cent. On the other hand, the incidence of penicillin reactions in the vaginal and rectal mucosa have been almost nil.

Epstein and Macaulay point out that if a reaction occurs during parenteral penicillin therapy, it does not necessarily indicate that penicillin may not be tolerated at a later date. Sensitivity may be of relatively short duration and may decline rapidly. It may decrease over a period of six to twelve months so that a second course may be taken without reaction. The interval may be shorter, but it is rarely less than six weeks. On the other hand, each subsequent attack may tend to increase the degree of sensitivity, with an increase also of the severity of the reaction. In these cases, the patient should be given small trial doses. The intradermal test may be positive and yet the patient may tolerate intramuscular injections.

THE CLINICAL PROBLEM IN PENICILLIN SENSITIVITY

Peck and his associates report their observations on tests for penicillin and trichophytin sensitivity in a group of 406 adults and ninety-one children.

Material Methods.—Intradermal tests:

(a) 0.01 to 0.02 c.c. of 5,000 units per c.c. amorphous penicillin; read in fifteen to twenty minutes for immediate reaction.

(b) 0.10 c.c. intradermal, 2,000 units or 1.2 mg. in .10 c.c. isotonic sodium chloride; delayed type of reaction is read in forty-eight hours or later.

If commercial amorphous penicillin is used, re-check positive reaction to crystalline penicillin. Amorphous preparations may give nonspecific reactions.

(c) Trichophytid test: 1-30 dilution in 0.10 c.c. isotonic sodium chloride.

The Delayed (forty-eight hour) Cutaneous Test.—This is a reliable index of penicillin sensitivity. The reaction is similar to the trichophytin test. A positive reaction is characterized by an area of erythema with edema and infiltration, usually about 1 cm. in diameter. It may be larger and studded with small papules or even vesicles. Local pruritus is common with the reaction. In some instances of high degree of sensitivity, positive reactions may be noted with 2 to 5 units.

The Patch Test.—This is not of much value.

Immediate Intradermal Test.—All reactions were negative on ninety-two subjects (Peck).

CLINICAL REACTIONS

According to Peck, two major types of penicillin reactions are most commonly encountered: (1) reactions of the urticarial serum-sickness-like type, in which sensitization is induced by treatment; (2) reactions with an erythematovesicular eruption, resembling the trichophytids.

Type 1. Reactions of the Urticarial Serum-sickness-like Type.—Urticaria and erythema with joint pains and sometimes fever, occurring after a definite incubation period (seven to twelve days), characterize the most common type of allergic reaction to penicillin. In some instances, reactions may occur within several days; in others, they may be delayed as long as three weeks. In severe cases, there may be angioneurotic edema, asthma, pulmonary infiltration and hyperpyrexia. Reactions occurring after the second or subsequent administration may be of the accelerated type, occurring with a short or no incubation period. Most reactions follow intramuscular injection, but may also follow oral administration.

Although a positive penicillin reaction is helpful in confirming sensitivity, a negative reaction does not exclude sensitivity. When several medications are administered, the test is useful in determining which drug is responsible for the eruption. The incidence of test skin reactions is greater in those patients who have had penicillin previously. In a group of ninety-eight patients, observed by Peck, who had received penicillin without reactions, not one reacted positively to the cutaneous test. Among 130 patients who received penicillin, seventeen (13.4 per cent) showed positive cutaneous reactions. Among those who had not had penicillin, the incidence of reactions was 5 per cent. All of the above seventeen patients who reacted were men (general ratio: 3 to 1). Positive reactions may become negative later. The majority of patients gave no history of allergy. The incidence of penicillin reaction is very low in children.

If the penicillin reaction has been mild, the readministration may be accompanied by epinephrine or antihistamine drugs. Substitute medication with sulfonamide drugs might be preferable. In sensitive patients, small doses of 2,000 to 3,000 units at six-hour intervals may be tried first, then gradually increased. It is unwise to give large doses in cases where previous reactions occurred or where positive cutaneous tests were present. On the other hand, induced sensitivity is only temporary, and a later administration may be well tolerated without reactions.

Type 2. Reactions with Erythematovesicular Eruptions, Trichophytid Type.—The latent stages characterized by a positive reaction in the absence of previous administration of penicillin.

The active stage is based on a pre-existing latent sensitivity. There is an erythematovesicular reaction which tends to localize on the hands, feet and groins. It may become a generalized exfoliative dermatitis.

MECHANISM OF SPONTANEOUS SENSITIVITY

Latent penicillin sensitivity is apparently associated with previous fungus infection. Skin sensitization to penicillin takes place in much the same way as sensitization to trichophytin.

DESENSITIZATION TO PENICILLIN

Desensitization before readministration of penicillin is more frequently necessary with Type 2 than with Type 1 sensitivity.

DESENSITIZATION SCHEDULE FOR SUBCUTANEOUS ADMINISTRATION (PECK ET AL)

Injection	*Number of Units*	*Intervals*
1	200	
2	400	Injections every 2 to 3 days.
3	800	
4	1200	Injections daily.
5	1600	
6	2000	May be necessary to
7	2500	
8	3000	start with 50 units.
9	5000	
10	10,000	With local reaction or fever,
11	15,000	
12	20,000	reduce dose to nonreactive point.

Oral Desensitization—Start with 1,000 units per day and gradually increase following precautions as recommended above.

ROUTINE TESTING OF OFFICE PATIENTS

As a matter of record, it is suggested that all new patients and all previous ones who return for observation should have the cutaneous test to penicillin. In the event that the administration of penicillin is necessary at a later date, one knows how to proceed with treatment and possibly avoid many severe reactions.

MANAGEMENT OF URTICARIA AND ANGIONEUROTIC EDEMA RESULTING FROM REACTIONS TO PENICILLIN SERUM AND OTHER AGENTS

While we are concerned for the moment with urticarial or serum-disease-like reactions to penicillin, the principles of treatment outlined below apply also to reactions from serums and other allergenic substances. These methods of therapy are also applicable to cases of unknown etiology.

The milder types of reaction may disappear very promptly without any treatment whatsoever. The more marked reactions usually respond to the administration of an antihistaminic drug or epinephrine.

The severe types, with generalized urticaria and angioneurotic edema as well as other complications, do not respond to the ordinary types of therapy; thus, more heroic and intensive types of therapy must be employed.

SPECIFIC IMMUNIZATION

For the treatment of acute urticarial reactions, Rinkel found that satisfactory relief could be obtained by the administration of 1 to 2 units of penicillin intradermally every one or two days.

HISTAMINE THERAPY

Based on a group of nine patients with severe foreign protein type of reactions (eight to penicillin and one to horse serum), most of whom failed to respond to other forms of therapy, Prince and Etter have reported their observations on the use of intravenous and intradermal histamine. All patients showed clinical improvement. It was pointed out that no definite dose or rate of medication can be established; each patient presents an individual problem.

Prince and Etter recommended the intravenous administration of histamine as the method of choice, as the dose and side effects can be readily controlled by the rate and amount of the infusion. All or part of a solution of 250 c.c. of saline or 5 per cent glucose, containing 2.75 mg. of histamine acid phosphate (1 mg. histamine base), is given at first to determine the patient's degree of tolerance. The rate of injection is regulated so as to produce a generalized flush. If given too rapidly, headache and substernal pain may be induced. The average interval between injections was found to be about six to eight hours. In some cases, continuous infusion or a stronger solution, such as 5.5 mg. per 250 c.c. of vehicle, may be necessary.

Intradermal administration was found to be very useful by Prince and Etter, especially in those instances in which intravenous therapy was not satisfactory, and also in patients in whom it was difficult to locate the veins and in the treatment of children. This method must be used with caution, as treatment cannot be discontinued at will as in the case of the intravenous. Small intradermal injections should begin with 0.10 c.c. of a solution containing 2.75 mg. per 5 c.c. (or 1-5,000) and increased as indicated. When larger doses are required, histamine dihydrochloride, 1-100, may be given in doses of 0.05 to 0.10 c.c. The idea is to determine the dose which will produce a flush for a period of one-half to two hours. When properly regulated, there appears to be no danger from the use of histamine therapy of this type.

This method of treatment requires hospitalization, and the therapy must be instituted by responsible personnel.

NONSPECIFIC TREATMENT WITH STAPHYLOCOCCUS TOXOID

Nonspecific therapy has always had a place in allergy, especially in those cases in which everything has been tried without results. It is a well-known fact that allergic reactions are counteracted by tissue injury or shock. A fracture, a burn, fever, a surgical procedure, a local or general reaction from a vaccine will produce this effect, as manifested, for

example, by the disappearance of urticaria, nasal allergy or bronchial asthma at least for an indefinite temporary period of time.

From time to time we have encountered many cases of severe acute and chronic urticaria and angioneurotic edema in which every therapeutic means of management was tried without satisfactory results.

After groping around among various possible nonspecific agents, it was decided to try small doses of staphylococcus toxoid.

Preparation Used.—
Staphylococcus Toxoid 100 units per c.c.
Dilute 1-10 as follows:
1 c.c. (100 unit stock) plus 9 c.c. saline = 10 c.c. — 10 units per c.c.
With 10 units per c.c. solution, 1 unit = 10 c.c.
Range of dosage: 1 unit to 20 units
Intervals: 3 to 4 days, later 7 to 10 days.

Treatment may be started with a dose of 1 to 2 units. If only slight or no effect is noted, this can be increased to 2, 3 or even 5 units. When the effective dose is determined, it is not changed, but the intervals are increased. If seven- to ten-day intervals are obtained with no symptoms, treatment should be discontinued.

In several instances of severe acute penicillin urticaria, 1 to 2 units were effective in giving relief within twelve hours. Sometimes only a few treatments are necessary.

In a patient with continuous urticaria of twelve years' duration, response was immediate to 20 units. The dose was immediately reduced to 1 or 2 units at five- to seven-day intervals. The patient is now free of symptoms after one month of treatment.

In another patient, a chronic urticaria of two years' duration cleared within one week. In several other cases of the chronic type, with no known etiology, response to treatment was satisfactory.

This method has been consistently effective in the relief of severe penicillin reactions, often requiring only a few injections at three- to four-day intervals.

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INHALANT ALLERGY

I. The Whealing Response of the Skin to Serial Dilution Testing

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IN 1941 Hansel[1] published an article on small pollen dosage which recreated interest in two phases of inhalant allergy.

First was the fact that certain patients could obtain relief with small doses. This was in contrast with the fact that many patients had received good results with the larger doses which had always been used. His findings not only indicated that inhalant allergies varied in degree in successive patients but implied that in the same individual sensitizations to the different antigens could be expected to differ. This clinical observation emphasized the need for not only determining to which inhalant the patient was sensitive, but to also ascertain the degree of each of these sensitivities. This can be done by some form of serial dilution testing.

Second, his paper stimulated further interest in coseasonal treatment.

In the course of a clinical appraisal of Hansel's method of titration and treatment with individualized dosage, I have employed serial dilution testing (titration) on every patient seen during the past eight years. In the course of this study certain features of the whealing response of the skin to such tests were revealed. I believe these are of sufficient importance to justify this communication.

TECHNICAL DATA

All our extracts are made in 50 per cent glycerine and Coca's solution.

Pollens are prepared for testing in genetic groups; all other inhalants are made up individually. No foods have been used.

The diluting fluid is normal saline with 0.4 per cent phenol added.

Dilutions are made in the ratio of 1:5 since these are more nearly approximate to the sensitivity of the skin than are the 1:10 dilutions. These solutions are made new every two weeks. It has been found by testing that there is a measurable deterioration by the fourth week and a possible loss of potency by the third week.

These dilutions are numbered from No. 1, the weakest, to No. 9, the strongest. The No. 1 is approximately a 1:40,000,000, and the No. 9 is a 1:100 dilution. The No. 10, or Concentrate solution, is a 5 per cent solution by weight volume. It has been shown by these tests that there is no essential difference between a 3 and a 5 per cent solution. In Table I, I have indicated the various dilutions, the number used to designate each dilution and the approximate dilution of the antigen in these different solutions.

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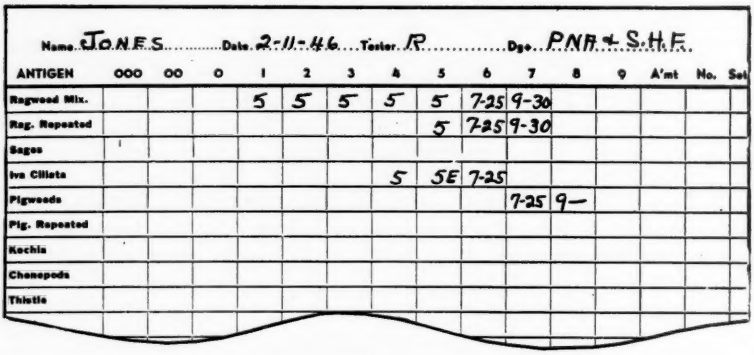
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ANTIGEN	000	00	0	1	2	3	4	5	6	7	8	9	A'mt	No.	Set
Ragweed Mix.				5	5	5	5	5	7-25	9-30					
Rag. Repeated								5	7-25	9-30					
Sages															
Iva Ciliata							5	5E	7-25						
Pigweeds										7-25	9—				
Pig. Repeated															
Kochia															
Chenopods															
Thistle															

Fig. 1. A special chart used to post results of testing. Wheals without erythema are posted with numerals indicating their size in millimeters. Wheals with erythema are posted with two numerals, the first indicating the size of the wheal, the second the amount of erythema.

TABLE I

Dilution	Number used to Designate This Dilution	Approximate Dilution of Antigen
Concentrate	10	1:20
1:5	9	1:100
1:25	8	1:500
1:125	7	1:2,500
1:625	6	1:12,500
1:3,125	5	1:62,500
1:15,625	4	1:312,500
1:78,125	3	1:1,562,500
1:390,625	2	1:7,812,500
1:1,953,125	1	1:39,062,500
1:9,765,625	0	1:200,000,000
1:48,828,125	00	1,1,000,000,000
1:244,140,625	000	1:5,000,000,000

In some instances it is necessary to use the 0, 00 and 000 solutions, but these are not ordinarily kept made up. They are not needed more than once or twice yearly, hence it would not be practical to either prepare them or to use them routinely. On one occasion I have had a patient respond with a 15 mm. wheal to the triple-zero dilution of house dust and be nonreactive to the control. The end point of reaction to pollen and animal danders varied between Solutions 4 to 8.

It has been found of great practical value to use numbers in reference to solutions rather than their actual numerical dilutions. Furthermore, it is easier to discuss this type of testing and the results when these solutions are numbered in the order of their application, rather than the oft used method of designating the strongest solution as No. 1.

The amount injected is 0.01 c.c. This will produce a 4 mm. wheal when injected at the proper depth. This wheal should be pale and sharply demarcated. The results of the tests are more apt to be modified by the depth of the injection than by inability to measure exactly 0.01 c.c.

Readings are made at the end of ten minutes and are posted on special sheets as shown in Figure 1. The negative responses are given in numerals indicating the diameter of the wheal in millimeters. This is

usually 5, sometimes it is 6. When the wheal is erythematous, instead of pale, but without a zone of erythema about it, this is indicated by the designation of 6E or 7E as the case may be.

When the reaction is characterized by a zone of erythema about it, this is indicated by using two numerals, separated by a dash. The first number refers to the diameter of the wheal, the second to the diameter of the erythema. A posting of 7-25 would mean then, that the wheal was 7 millimeters and the erythema was 25 millimeters in diameter. If one does not wish to post erythema, its occurrence is indicated by using the numeral for the wheal, followed by a dash, as for instance, 9—.

Occasionally tests increase in size between ten and twenty minutes, and when so, these are posted with the letter "D" before the numerals, for instance, D11-30. These late and increased reactions are considered under certain conditions. Some patients will always show an increase after ten minutes; others never do, and still others will show this only with certain antigens. It has been found that when the end point moves from one dilution to another in delayed reactions they are of significance. If one is in doubt, err on the side of accepting the weaker reactor as being the end point. These delayed reactions are found mostly on original pretreatment testing.

Finally, and this is extremely important, the testing and the therapeutic solutions are to be made from the identical lots of the same material.

TYPES OF RESPONSE TO SERIAL DILUTION TESTING

All reactions may be classified under two distinctive forms. First are those having one or more absolutely negative tests, followed by a distinct reaction of whealing, erythema and then progressive whealing, usually through three dilutions. This is called the clear-cut end point type of reaction.

The second form of response has erythema with every test applied.

Tests with Clear-Cut End Point of Reaction.—In this type of reaction there will be one or more tests which have given a 5 mm. wheal without erythema, and then the next stronger dilution will produce a reaction characterized by two features: first, there is a zone of erythema about the wheal, and second, the wheal is 7 millimeters in diameter (or two millimeters larger than the non-reactor or the control). The next two tests will invariably show progressive whealing, usually being 9 and 11 millimeters in diameter, but the erythema remains about the same. This type of response is illustrated in Figure 2,A. This is the nature of the skin response in approximately 72 per cent of all tests applied in our patients.

There may be deviations from this "normal" response, either in the wheal size or in the occurrence of the erythema. For instance, one may obtain a response of several 5's, then get 6-20, 8-30 and 12-30. Again,

one may have a response of several 5's, then get 5-20, 7-25, 9-30 and 11-30 (Fig. 2,B).

Whealing is invariably progressive with the first three dilutions, including the one producing the end point of reaction, but in some cases there

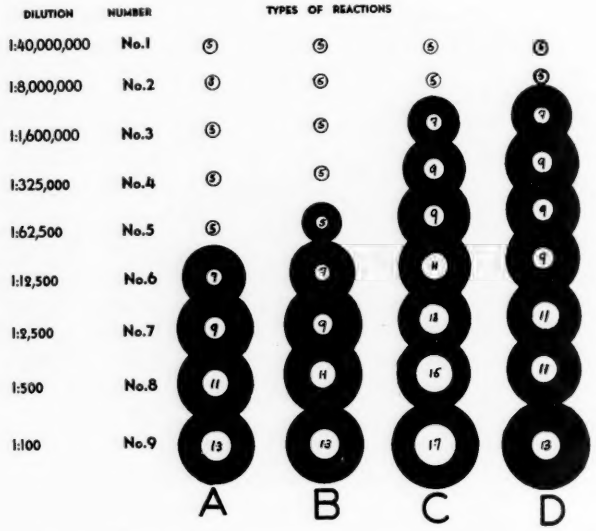

Fig. 2. A diagrammatic representation of reactions with clear-cut end points. (A) End point with both erythema and 7 mm. wheal occurring on same dilution. (B) End point with erythema occurring with 5 mm. wheal, followed by 7-25 reaction and progressive whealing. (C) End point with both erythema and 7 mm. wheal occurring on same dilution, but whealing is identical on the second and third reacting dilutions. This is a short plateau. (D) End point with both erythema and 7 mm. wheal occurring on same dilution, with identical size wheals on the next three dilutions. This is a long plateau.

are one or more 5's, then 7-20, 9-30, 9-30 and then 11-30. This phenomena of different strength solutions causing identical sized wheals is called the plateau of the reaction, and it may be short (Fig. 2,C) when due to two dilutions, or it may be long when due to three dilutions or even more at times (Fig. 2,D). These two reactions suggest concomitant and complicated sensitizations. These are often, but not necessarily always, associated with food allergy.

Reactions with Erythema on All Dilutions or Linear Erythema Responses.—As the name suggests erythema is present on the first test applied, regardless of the wheal size. There are several modifications of this type of reaction.

1. Straight linear erythema response: In this reaction there are several tests all reading 6-25 or 7-25 and then there is an 8-30 or a 9-30 reaction followed by progressive whealing. The end point of reaction

in this test is the dilution which initiates progressive whealing (Fig. 3,A). This reaction is not due to dermographism since one can obtain both the clear-cut end point type of reaction and the linear erythema response side by side at the same time in a given patient. Actually, only 3 per

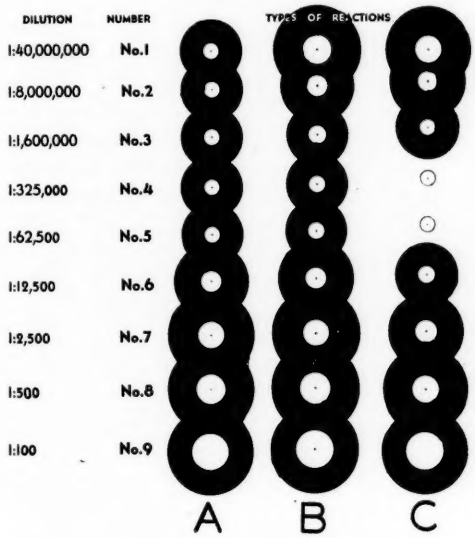

Fig. 3. A diagrammatic representation of responses with erythema on the first test applied. (A) Straight linear erythema response, having several identical size wheals and then develops progressive increase in size of wheals. (B) Hour-glass linear erythema reaction, whealing and erythema having the configuration of an hour glass. (C) Hour-glass linear erythema response with clear central zone.

cent of the patients have dermographic skins; that is, every test applied including the control has erythema about the wheal.

2. The hour-glass linear erythema response: In this test the configuration of the erythema and the wheals simulates an hour glass. The usual readings are, 12-35, 9-30, 8-25, 7-25, 7-25, 9-30, et cetera. The end point of reaction is the 9-30 reaction (Fig. 3,B).

3. Hour-glass reaction with clear central zone: This reaction is not due to technical error as I first thought (Fig. 3, C). There is decreasing whealing and erythema for several dilutions, then one or more tests with absolutely no reaction, then progressive whealing with erythema. The end point of reaction is the first solution producing whealing and erythema after the clear zone.

TERMINOLOGY

Two terms which have been used in this communication should be defined in more detail.

First is the "end point of reaction." This may be defined as being

the first dilution which initiates progressive whealing and *is also* 2 millimeters larger than the preceding or the non-reacting tests, one or the other, as the case may be. In the clear-cut end point reactions this test will usually be the first to show erythema, unless erythema is obtained with a 5-20 reaction, then it would be the first wheal to attain the 7-20 size. In the linear erythema reactions the end point is the first solution to initiate progressive whealing. In the hour-glass reactions with the clear central zone it would be the first solution below the clear zone *which is followed by* progressive whealing.

The second term is the "multiple" or as often stated, "the multiple of the end point." To obtain this, the treatment dose is computed in terms of the solution giving the end point and then is divided by the test dose. (This is always 1.) Example: If the end point was on the No. 6 dilution and the dose is 0.10 c.c. of the No. 7 dilution, this would be a multiple of 50. (0.10 c.c. of the No. 7 would equal 0.50 c.c. of the No. 6 solution.) The multiple of 50 when the end point is on the No. 6 solution could be any of these four doses: (1) 2.50 c.c. of the No. 5, (2) 0.50 c.c. of the No. 6, (3) 0.10 c.c. of the No. 7, or (4) 0.02 c.c. of the No. 8.

If the end point is on the No. 3 dilution and the patient is receiving 0.25 c.c. of the No. 5 dilution, this is equal to 6.25 c.c. of the No. 3 solution; hence the multiple is 625.

The statement of the treatment dose in terms of the "multiple" is a convenient means of giving the therapeutic dose in relation to the end point of reaction and is a comparative expression of the end point of reaction and the necessary dose.

SUMMARY

The clinical implications of the types of response to serial dilution testing should be so obvious as to require little explanation. However, certain points might be emphasized.

The clear-cut end point reactions present little error in interpretation. One should not mistake the occurrence of erythema without a concomitant increase of whealing as the end point of reaction.

The possibility of making an important clinical error in the interpretation by using only a single or two solutions in testing is more likely in the case of the linear erythema reactions.

In the case of the hour-glass reactions, with a 12-30 response on the No. 1 dilution and only a 7-25 on the No. 5, one could interpret this large initial whealing of the skin to indicate a very high degree of sensitization if the various types of skin response are not known. It can easily be seen that the results of therapy based upon such misinterpretation of skin testing would be ineffective.

It would seem that the minimal requirement in the use of intracutaneous

(Continued on Page 650)

INHALANT ALLERGY

II. Factors Modifying the Whealing Response of the Skin

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IN A PREVIOUS communication[2] the nature of the whealing response of the skin to serial dilution testing was described in detail. In this paper the factors which modify this response will be discussed in light of our present knowledge.

TERMINOLOGY

There are four terms used in this paper which should be delineated at this time.

First is that of "vertical testing." This refers to the application of tests of various antigens, all of the same numbered dilution. Normally, this is done in preseasonal testing, but may also be done in coseasonal application of serial dilution tests (titration). It refers to the fact that the same strength material is used of *several different* antigens.

Second is that of "linear testing." This refers to the application of various numbered dilutions of the same antigen. This is the usual procedure when one is attempting to determine the end point of an antigen.

Third is that of "shift to the left." This term is used when the end point moves towards the No. 1 dilution.

Fourth is that of "shift to the right." This term is used when the end point moves towards the No. 9 dilution.

TREATMENT

Treatment, or so-called hyposensitization, is the most definite single factor which affects the whealing response of the skin. The effect of therapy may be either very rapid, often with one or two doses, or it may be gradual, such as occurs with the generally accepted plan of dosage over a period of time.

The effect of specific treatment upon the whealing produced by an antigen will vary according to the time when an evaluation is made of such possible effects. In this discussion, the figures have reference to ragweed and pigweed sensitive patients in seasons, after treatment with their primary and secondary pollen allergies. It has been found that under these conditions approximately 43 per cent of the patients have a definite decrease in their whealing response. At times the end point will shift one or two dilutions to the right. Approximately 36 per cent have no particular change in their test reactions, while 21 per cent have a definite increase in their whealing, or a shift to the left, sometimes as much as five dilutions.

In the preceding paragraph the changes discussed were those which oc-

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curred after preseasonal treatment with continuation of coseasonal therapy until the tests were repeated. These are, therefore, the results of prolonged treatment. There is, however, a somewhat more dramatic and rapid effect, which when it occurs with one or two doses is termed "flash response."

The term "flash response" refers to reactions as illustrated in the following case reports: A patient was tested with the No. 8 dilution of pigweed out of the pollen season and without any previous therapy. The reaction was a 13-45 response in ten minutes. This would ordinarily be evidence of a high degree of sensitivity, but when the weaker dilutions were applied the following day, it was found that there was no reaction until the No. 7 dilution, and a repetition of the No. 8 dilution only produced a 9-30 reaction. This then is a "flash response."

A second patient gave a 35 mm. wheal to the No. 8 dilution of Alternaria. When linear testing was done, the end point was found on the No. 4 solution. There is a discrepancy of 20 mm. between the No. 8 test of the first day and the end point. This, too, is a "flash response."

"Flash responses" concern not only those who titrate but also those who use ordinary scratch tests. It is imperative to have all scratch tests repeated. The second day's tests are more likely to reflect the actual degree of sensitivity.

It would seem that there are two phases to the whealing response of the skin to either scratch or intracutaneous tests. One is a somewhat evanescent reaction which is responsible for the reactions described above. The other is a more or less fixed or less flexible phase of the reaction. It seems quite evident in terms of our experience that treatment should be based upon the more fixed phase of the skin whealing response. Failure to take this phenomena into consideration has no doubt accounted for a great number of the failures in the previous use of the method of therapy discussed in Hansel's paper.[1]

Finally, only 7.7 per cent of the patients examined in complete detail during two seasons showed no significant change in the whealing response to any of their inhalant allergies.

INHALATION OF POLLEN

The inhalation of either the primary or secondary pollens may modify the whealing response of a given inhalant. In one case the end point of ragweed shifted from the No. 7 to the No. 2 dilution when the patient was retested four days after kochia and fourteen days after pigweed had started to pollinate. This reaction represents an increase of 3,125-fold in the whealing response. This patient gave evidence of clinical sensitivity which was parallel with this increase in skin sensitivity. It should be noted that this increase occurred before ragweed had come into the air; hence this effect was due to so-called secondary pollen, that is, pollen which did not initiate symptoms of pollinosis, yet did produce skin reactions.

In another case there was no shift to the left until after the patient had inhaled the primary pollen, ragweed, for ten days. However, this patient was also sensitive to pigweed and kochia without having evidence of pollinosis until the ragweed season.

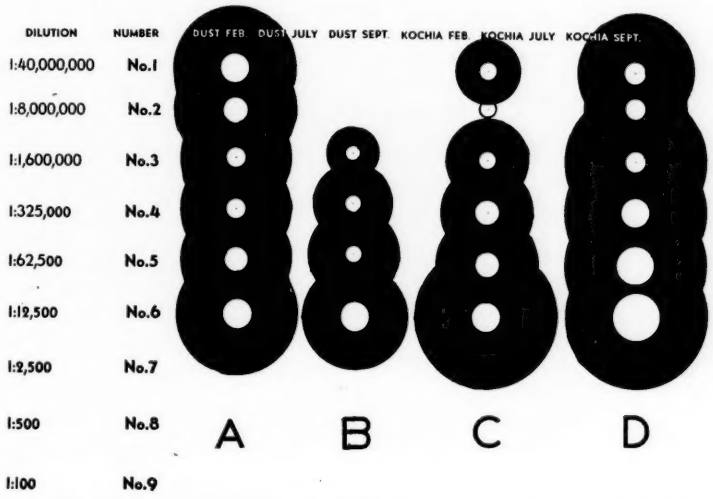

Fig. 1. A diagrammatic representation of whealing response in relation to specific foods having a concomitant effect. (A) Ragweed tests with wheat in the diet. (B) Repetition of ragweed tests on the fifth day after elimination of wheat. (C) Reaction to ragweed when oysters had not been used for days. (D) Response to ragweed sixteen hours after ingestion of oysters, which produced both hay fever and asthma during ragweed season.

In another patient sensitive to elm pollen there was a shift of the end point from the No. 9 to the No. 7 dilution, one week after the start of elm pollination.

In connection with this shift to the left of the end point in the pollen season, emphasis should be placed on the fact that there are not just a few, but a good number of patients who have a positive skin test to a specific pollen in the pollinating season only. Therefore, if there are pollen groups in the patient's community to which the patient did not react out of season, the patient should not be assured that he is not sensitive to these inhalants. Should a patient have a recurrence of hay-fever symptoms in spite of treatment, it is necessary to recheck with those pollens which are airborne at that time and which did not give a reaction in preseasonal testing.

In one case a patient was tested on June 28 with pigweed and kochia as well as all other pollen groups in our area. Both of these tests gave only a 5 mm. wheal on the No. 9 dilution. Two weeks after the onset of pigweed pollination he reported the recurrence of hay fever which concurred with the onset of pigweed hay fever in known cases of this allergy.

A recheck of the No. 8 and the No. 9 solutions produced a reaction of 15-55 and 17-60, respectively. In many of these cases the maximum reaction is only a 7-25 response on the No. 9 dilution.

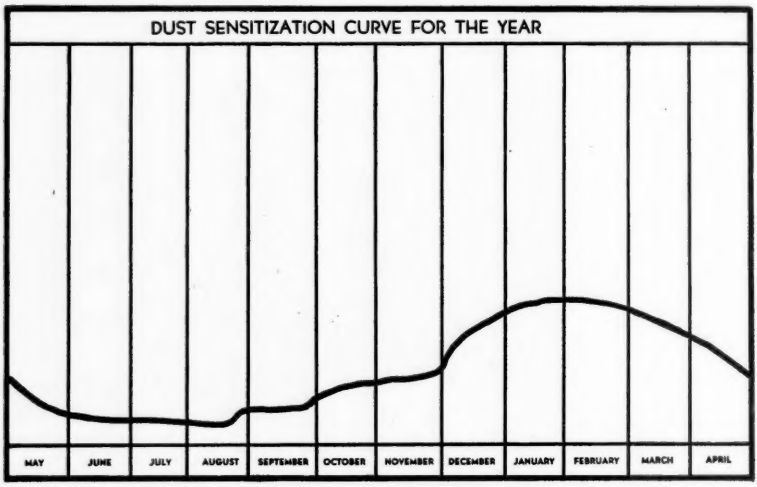

Fig. 2. Dust sensitization curve for the year, as determined by the occurrence of the end point of reaction in a series of patients. Abrupt increases occur with pollination of short ragweed and the advent of cold weather; progressive increases occur after the cold season to the peak of the year, in the last of January or early February.

THE EFFECT OF CONCOMITANT FOOD ALLERGIES

The ingestion of foods having a concomitant effect will do two things: first, they often make reactions erratic, and second, they often increase the whealing response. Figure 1, A is a diagrammatic outline of the response to ragweed with wheat in the diet. In Figure 1, B the response to ragweed is shown when the tests were repeated four days after the elimination of wheat.

In another patient with a concomitant reaction to oysters, tests were made when they had not been used for weeks. The reaction is shown in Figure 1, C. When the tests were repeated sixteen hours after eating oysters, the response had changed to that shown in Figure 1, D.

FACTORS INFLUENCING DUST SENSITIVITY

The seasonal variation in the degree of sensitivity to house dust is depicted in Figure 2. This has been determined by establishing the end point of reaction at different seasons of the year in a large series of patients.

It will be noted that the low point of sensitivity occurred during the summer months. There is an increase at the end of August with the advent of short ragweed pollen. Again, there is a more definite increase

with the first cool days in late September. This increase will occur in some patients only two or three days after it is cold enough for houses to be closed and furnaces turned on. There then follows a

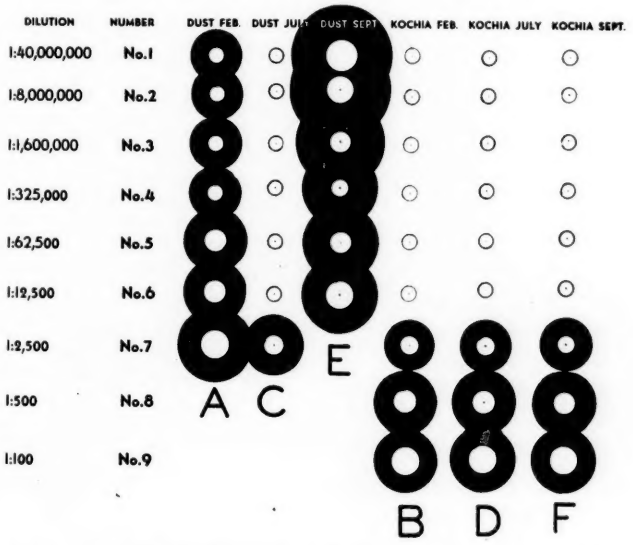

Fig. 3. Dust and kochia reactions in different seasons. (A) Dust, and (B) kochia, in February before treatment. (C) and (D) Dust and kochia a few days after start of kochia pollination. (E) and (F) Dust and kochia two weeks after start of short ragweed pollination. Note that the kochia end point did not change in any season, while dust did, and the recurrence of symptoms coincided with advent of these two pollen seasons.

gradual increase in sensitivity until the third week of January, which is the peak of the year. There is, however, a significant change early in December. This is the time when many patients have dust symptoms in spite of treatment. The most logical explanation is that these patients have sufficient discrepancy between their dose and their degree of sensitivity at this time so as to make therapy ineffective. It has been found that this seasonal breakdown is more dramatic in some years than others.

Since therapy should be in terms of existing sensitivity, it is necessary to retest dust cases at such times so as to precede a clinical breakdown in therapy. It has been found very beneficial to do this in all dust cases during the first week of December, or sooner if the patient shows evidence of therapeutic failure.

There is another phase of dust sensitivity which is of particular importance in patients with pollinosis. In Figure 3, A and B indicate the end points to dust and kochia in February. Dust and pollen therapy was effective until the first day of kochia pollination. A retest of the patient at that time is shown in Figure 3, C and D. When the dust dose was ad-

justed in terms of current sensitivity, the patient again had relief. It should be noted that the kochia and ragweed end points have not changed.

After short ragweed came into the air, the patient had a recurrence of

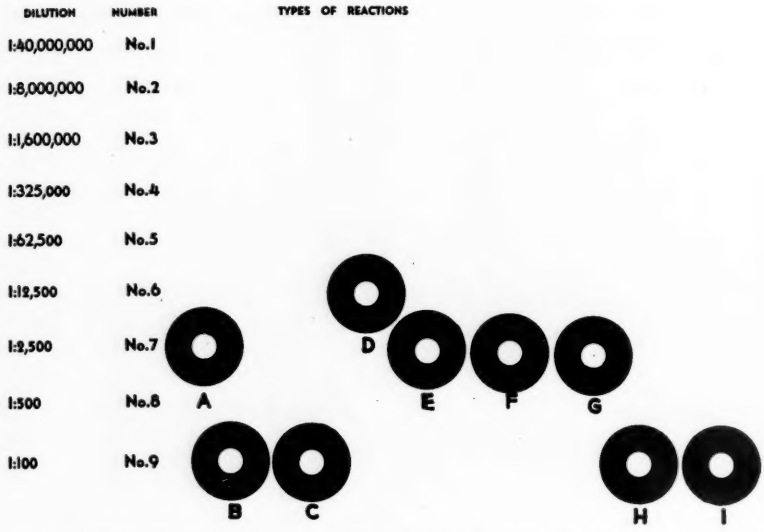

Fig. 4. End point of reaction to dust (A), elm (B), and grass (C), before treatment and before elm pollination. (D) Dust end point in elm season. (E) and (F) Elm and grass, respectively. (G) Dust end point in grass season. (H) and (I) The elm and grass end points.

symptoms, and a retest was made on September 10. This is shown in Figure 3, E and F. One may note that the dust sensitivity has increased, but kochia and ragweed have not changed. Therapy, in terms of current dust sensitivity, again relieved the patient. The influence of dust sensitivity in connection with the pollen seasons has been observed in a good number of patients who are sensitive to dust.

THE INFLUENCE OF TREE POLLEN ON WHEALING

Tree pollen is very prone to affect the whealing response, not only of its specific tests but of other inhalant groups. In Figure 4, A, B and C show the results of testing dust, elm and grass on January 25.

The patient received thirteen days of complete relief of asthma with a multiple of 50 on dust. This dose was repeated three days after elm started to pollinate, with no certain effect, but it might have increased his symptoms. The tests were repeated, and it was found that the end point of dust was now on No. 6, as shown in Figure 4, D, E and F. It may be noted that elm, grass and dust have all shifted to the left. He was again relieved when the dosage was adjusted in terms of current sensitivity. On the first day of grass pollination his symptoms recurred, when he was

tested again, with the results shown in Figure 4, G, H and I. It will be seen that dust, elm and grass have all gone back to their original end points.

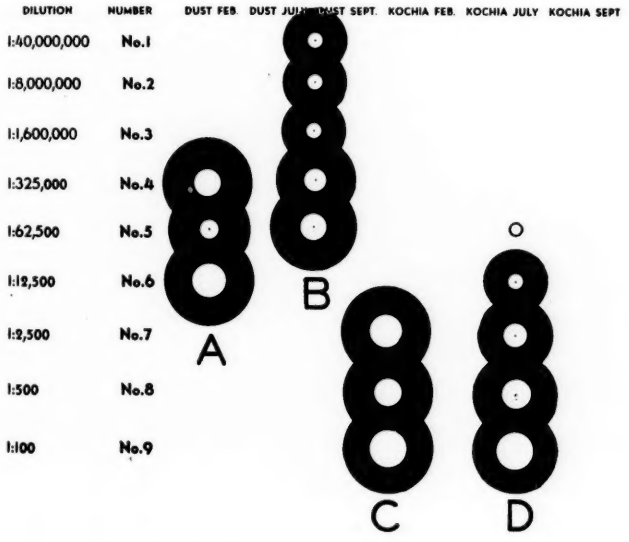

Fig. 5. Effect of overdosage or too strong initial test dose. (A) Overdosage of silk case with initial tests too strong. (B) Same tests applied four hours later, beginning with weak dose and advancing. (C) Testing with dust, with first dilution too strong. (D) Repetition of tests, beginning with weaker dose and increasing.

Tree pollen is particularly liable to cause these changes or to produce synergistic local reactions, misleading one in estimating the correct dose.

THE EFFECT OF OVERDOSAGE OR NONTREATMENT

Either overdosage or nontreatment are clinically the same as far as the patient's response is concerned. In Figure 5, A, the result of a silk titration is shown in a patient who had been overdosed. The tests were below the amount of the dose regularly given. Yet, it will be noted that the first test produced a 12-45 reaction, the second only an 8-45, and the third a 13-45.

In Figure 5, B, the results are shown of testing when the initial test was well below the end point and advanced to demonstrate progressive whealing. The significance of this second response was attested by the fact that the patient obtained ten days of relief with a multiple of 50 of this end point.

THE EFFECT OF EXCESSIVE INITIAL TEST DOSE

An excessive initial test dose is an overdose in terms of whealing response and relief of symptoms. In Figure 5, C are the results of applying the No. 7, the No. 8 and the No. 9 dust tests. It will be noted that these wheals are 11–, 8– and 12–, respectively. It can be stated almost as a rule that if the initial test dose is capable of producing a 10 mm. wheal or more, the next stronger dilution will give a lesser response and then increases will occur. When such results are obtained, one should repeat the tests starting below the level of reaction and advancing to the end point. The results of this technique for this case are shown in Figure 5, D.

It is imperative, if one wishes to establish the true end point of reaction and the actual whealing response, that tests should begin below the dilution producing any response.

SUMMARY

The whealing response of the skin may be reduced either rapidly or slowly by treatment. It may increase with the inhalation of either the same antigen or a so-called secondary factor, either inhalant or food. Tree pollen is particularly prone to produce increases in degree of whealing response. Excessive initial tests often give an erratic reduction in the first successive test.

When one knows the forms of whealing response to serial dilution testing and the factors which modify this, he is then prepared to apply this method of testing in clinical practice.

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PROCEDURE FOR DETERMINATION OF AEROSOL DELIVERY AND STABILITY DURING NEBULIZATION

(Continued from Page 618)

by oxygen, is comparatively stable, provided sufficiently high concentrations are employed. Suggestions for the clinical application of these results are provided which demonstrate how time of therapy may be shortened, with a marked increase of the material delivered by the nebulizer.

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INHALANT ALLERGY

III. The Coseasonal Application of Serial Dilution Testing (Titration)

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THIS TECHNIQUE was presented in part before the Southwest Forum of Allergy at Houston, Texas, in 1946, by Whitney Boggs, Michael Brodkey, Fannie Lou Leney and the author.[2] Since that time there has been considerable improvement in both the fundamental knowledge and the clinical application. This communication presents the method as currently employed by a number of allergists.

PHYSICAL FACILITIES

The physical facilities are important. I use a special table mounted on casters so that all equipment can be moved from room to room. It has a stainless steel holder for the syringes along the back side, with the rinse solutions behind and slightly below the tops of the syringes.

The rinse solutions are as follows: (1) Two per cent salt and 1 per cent sodium bicarbonate with 0.4 per cent phenol. This is colored with a drop of aqueous saffron. (2) Seventy per cent alcohol, to which a slight trace of gentian violet is added. (3) Normal saline with 0.4 per cent phenol. This solution is not colored. The purpose of coloring solutions is to prevent mixture or error.

Syringes are rinsed following each test. Two may be held at a time, and three rinses are made in the first solution by filling the syringes to at least the 0.60 c.c. mark. Then two rinses are made in the alcohol, and finally, two rinses in the third solution. The inspirated material of Solutions 1 and 3 are disposed of in a waste bottle. The alcohol is returned to its container and is filtered daily. This technique has been found adequate in both terms of sterility and contamination of antigens.

One syringe is used for each antigen. Both the syringe and its holder are labeled. This label is gummed on and then painted over with a mixture of Dupont Household Cement and amyl acetate. Syringes are arranged from right to left to correspond to the occurrence of seasonal pollination. This is not only a matter of personal choice but has great practical value, for all of the pertinent pollen groups for any one season are grouped together.

In the application of the tests, one can work best seated, with the patient on a chair or stool about 5 inches higher than one's self. It is best to use a posture chair which swivels and is mounted on free rolling casters. The application of the five tests usually run at a time are made in thirty-five seconds when a nurse assists with syringes.

It is important to keep tension on the skin so as to make accurate in-

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sertion of the needle more certain. This will produce sharply demarcated wheals and will also give one a closer judgment of the amount injected. Originally, the exact amount to be injected was measured, but

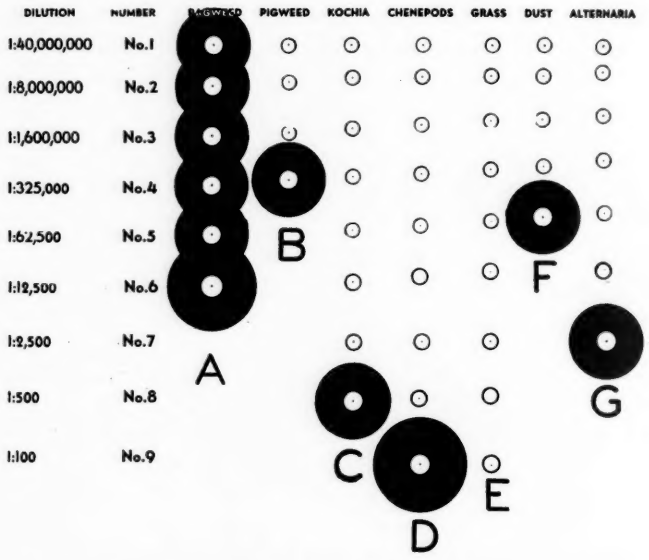

Fig. 1. Diagrammatic representation of testing and end points of reaction in coseasonal application of titration technique. (A) Linear reaction to ragweed with end point on No. 6. (B) End point to pigweed on No. 4 solution. (C) End point to kochia on No. 8 dilution. (D) End point to chenopods, which is on No. 9 dilution. (E) Grass tests which failed to react. (F) End point to dust on No. 5 solution. (G) End point of Alternaria reaction on solution No. 7.
Note that testing is discontinued after establishing the end point of a specific product.

after experience it was found possible to make a correct injection by observing the size of the wheal. This will be 4 mm. when given at the correct depth.

Four patients can be tested at a time when there is an assistant. Timing is by individual clocks, using a ten-minute interval for readings.

This method of testing may be used either preseasonally or coseasonally, but only the latter method is considered in this communication.

COSEASONAL TECHNIQUE OF TITRATION TESTING AND THERAPY

This method is, I believe, the one of choice when the patient reports for care in the season with symptoms.

Testing is started with the No. 1 solution of the entire group of inhalants which could cause the patient symptoms during the season when he suffers from pollinosis. This will vary with the areas in which the patient resides, but in our location it will include at least ragweed, pigweed, kochia, chenopods, grass, dust and Alternaria, and Hormodendrum.

Figure 1 shows the results of testing when a patient with ragweed hay fever in our locality is studied by this method.

In this illustration it will be noted that as the end point of reaction is obtained with each antigen, it is dropped from the testing. It will be seen that ragweed produces a linear erythema response. The choice of continuing tests with ragweeds is based on this fact. The occurence of a

TABLE I. SCHEDULES AND MEASUREMENT OF MULTIPLES COMMONLY USED

Dose No.	Multiple Value of This Dose	Dilution Used
		End Point Dilution (For ex: No. 6)
1	15	0.15 c.c.
2	25	0.25 c.c.
3	35	0.35 c.c.
		Next Stronger Dilution (For ex: No. 7)
4	50	0.10 c.c.
5	75	0.15 c.c.
6	100	0.20 c.c.
7	150	0.30 c.c.

7-25 reaction on the No. 1 solution of ragweed may be either the end point of reaction or it may indicate the existence of a linear erythema response. Since this is the primary pollen (initiates the clinical symptoms) and the initial dose is a multiple of 15, one can safely apply the No. 2 ragweed dilution. This test is only a multiple of 5. When this is done, the occurrence of another 7-25 reveals the presence of a linear erythema response, and one can safely continue to apply the next stronger dilution every ten minutes until a wheal larger than 7-25 is produced. This occurred in this case on the No. 6 dilution. The end point of pigweed was found on the No. 4 dilution, dust on the No. 5, Alternaria on the No. 7, kochia on the No. 8, and chenopods on the No. 9 dilution, respectively. Grasses did not react.

Having established the end point of reaction to each antigenic group, therapy was started with the antigens which ordinarily could contribute to this patient's symptoms. In this case every reactor is airborne during the ragweed season; hence they all were used.

On the first treatment it has been found both safe and clinically of benefit to administer a multiple of 15 of the primary antigen, which in this case is ragweed.

The primary antigen is always kept separate, and the so-called secondary inhalants—the pigweeds, kochia, chenopods, dust and Alternaria—*may*, if one chooses, be put in a mixture as described herewith.

There is no means of determining by these or any other skin tests which dose is optimum, but in this area a multiple of 50 has been the most common satisfactory multiple. It is in keeping with this finding to make a secondary set in which all antigens appear in a multiple of 50. As can be seen in Table I, a dose can be increased to three times this multiple without any difficulty.

In making these mixtures it is best to reduce the multiple of 50 to the smallest amount of the strongest dilution which it is feasible to measure.

The end point dilution, the dose which is a multiple of 50, and the amount and dilution to be used in the making of the secondary set are all shown in Table II. Attention is called to the fact that with chenopods where the end point is on the No. 9 dilution, the multiple is not more than 20, since this has been found best in this type of reaction. The total amount of this dose, when expressed in the smallest amount of the strongest solution

TABLE II

Antigen	End Point Dilution	Amount and Dilution Equal to Required Multiple for Antigen		Volume Used in Set
Pigweed	4	0.02 c.c.	No. 6	0.16 c.c. No. 6
Dust	5	0.02 c.c.	No. 7	0.16 c.c. No. 7
Alternaria	7	0.02 c.c.	No. 9	0.16 c.c. No. 9
Kochia	8	0.02 c.c.	No. 10	0.16 c.c. No. 10
Chenopods	9	0.04 c.c.	No. 10	0.32 c.c. No. 10
Totals		0.12 c.c.		0.96 c.c. of the mixture

feasible to measure, is 0.12 c.c. This figure is important since it represents the volume of the 1:5 dilution of this mixture which is a guide to the beginning dose of the secondary set. The first dose is selected from the regular schedule shown in Table I, which is just below this amount, and then one advances through the two dilutions according to the posted schedule of doses. For instance, the first dose less than 0.12 c.c. is 0.10 c.c. Therefore one starts with 0.10 c.c. of the 1:5 dilution of this secondary set, which is being made especially for this patient. If the amount had been 0.18 c.c., one would start with 0.15 c.c. of the 1:5 dilution.

As the various amounts indicated in the right-hand column in Table II are measured out, they are placed in a common vial which is labeled the patient's concentrate vial. Multiplying the reduced dose by 8 gives sufficient quantity of material to make a 1:5 dilution and also to advance the dose in the concentrate dilution to its maximum amount, or even more if needed.

On the second treatment one administers a multiple of 25 of the primary antigen and a quantity of the 1:5 dilution of secondary set which is computed as described above. These are given together, since there is no local reaction as a rule and nothing is to be gained by giving the patient two injections. Therapy is advanced according to the schedule given in Table I and repeated as the dose wears off, guiding all features by the clinical response. The rate of increase may be subject to individual variation as seems best in each case, but deviations from this schedule have seldom been of benefit in the respiratory allergies, unless other factors are active. This will be discussed later.

It should be noted that one may measure the same multiple by using different amounts of two different solutions, but it has been found best to have the volume of the injection around 0.50 c.c., a point which Hansel[1] first made.

It is highly important to estimate rapid change in whealing response to antigens, particularly the primary one. In one case it was found that

the end point moved from the No. 6 to the No. 7 dilution after the first treatment, which was a multiple of 15 and gave one and a half days of relief. Therefore, the second dose, instead of being 0.25 c.c. of the No.

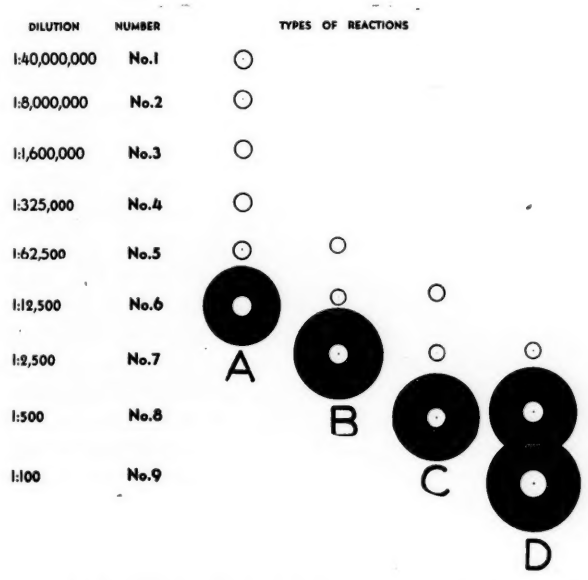

Fig. 2. Change in the end point of reaction as the result of treatment (A) Test with ragweed before treatment. (B) Testing following first therapeutic dose of ragweed. (C) End point after second ragweed treatment. (D) End point after third and successive treatments.
The importance of the shifting of the end point of reaction is depicted in this case, which if undiagnosed would lead to failure of coseasonal treatment.

6, was 0.15 c.c. of the No. 7 dilution. On the third visit the end point had moved to the No. 8 dilution, and then 0.15 c.c. of the No. 8 was given; while on the fourth visit there was no change in the end point, and then 0.25 c.c. was given, which is the second dose of the primary antigen.

In repeating these tests, one should limit his tests to a range that is less than the expected therapeutic dose. For instance, on the second visit a dose of 0.25 c.c. of the No. 6 dilution was in order. This was equal to 0.05 c.c. of the No. 7 and to 0.01 c.c. of the No. 8 dilution. Therefore, it would have consumed more than the correct second dose to have applied tests with Nos. 6, 7 and 8 solutions. For this reason the Nos. 5, 6 and 7 dilutions were used. It should be borne in mind that some of these patients increase in sensitivity with treatment; therefore, one ordinarily tests with three dilutions: one weaker than the last end point, the one giving the previous end point, and one solution stronger. The results of such testing are shown in Figure 2.

SELECTION OF ANTIGENS

It might be argued that if a patient does not have hay fever except in the ragweed season that he need only be treated with the ragweed pollen. This has not proven to be the best procedure in our area. It has been found repeatedly that treatment with a single antigen may be very effective the first year, but in successive years it has been necessary, with but few exceptions, to add the other products to which the patient is sensitive and which are in the air during his seasonal symptoms. It becomes increasingly difficult to define with accuracy what is or is not a secondary pollen. Furthermore, several of these pollens reach their peak of pollination in the ragweed season, and one should not assign all these cases to ragweed without very careful study.

It has been our custom to adequately test and treat these patients. When treatment is started with the primary antigen and the secondary mixture, one should continue to use them together, or always separate (i.e. on different days), but one should not change the schedule or omit one for a while. In some cases there appears to be a synergistic effect between certain pollens, and this effect cannot be gauged accurately if some doses are given alone. Again, there are certain individuals who cannot take the necessary dose, as determined either by titration or clinical results, until the primary and secondary products are separated. This is particularly true of tree pollen and dust injections.

ERRORS IN COSEASONAL TREATMENT

One must always be alert for the possibility of error in applying coseasonal therapeutic measures. The most important of these is a shift of the end point. It has proven to be of great help to repeat tests to establish the stabilized end point. This has never been found to exceed three times. It only requires three tests and one minute of time to apply them, a waiting time of ten minutes and a few seconds to read the tests.

The next most common error is overdosage, which is done by repeating and increasing the dose according to a fixed schedule when the patient does not get relief with a certain dose. If there is no definite relief with a multiple of 35, one should find out immediately what is wrong. I have never obtained relief with an increased dose if there was none with a multiple of 35, unless some other phase of treatment was corrected.

The third most frequent cause for failure is the attempt to build the dose to the point where the patient is getting a week's relief, simply because some other patient had been advanced successfully to that dose. I have had patients whose maximum period of relief was three days, others three weeks, with the same multiple. Patients whose end points are in the No. 1 to No. 4 dilutions are not likely to be given a full week's relief, yet those reacting on the No. 8 to No. 9 solutions are often able to go ten days in season, some two weeks and a few even three weeks.

In advancing doses from a multiple of 15 to 150 by the schedule given

in this paper, one must keep in mind that if all other causes have been evaluated, that failure to obtain a period of relief is the earliest evidence of overdosage. The earliest evidence of overdosage is not a constitutional reaction but the continuation of symptoms following a therapeutic dose.

Finally, the causes for failure are those of dietary complications. During the past three seasons I have kept a hay-fever patient in my home so that I might more fully evaluate what happens to these treated patients. It has been found that he obtained relief, *proportionately to the correctness of his diet,* when *all* inhalants were evaluated by titration. However, he was not relieved, even by diet, until he was treated for silk sensitization and for house dust allergy. He suffered severe limbic conjunctivitis with intolerable pruritus until his dust dose was adjusted.

CONCLUSION

If in the coseasonal application of titration technique and therapy one fails to get the desired relief, he should re-evaluate the degree of the sensitizations. If he is in doubt as to the dosage, begin again with a multiple of 15 and advance the dose. If the end point is on the No. 9 dilution, it might be well to start with a multiple of 5, although this is only occasionally of benefit. If this is done without benefit, then it would be logical to look for complicating sensitizations, first in foods and then in rare inhalants.

The presence or absence of limbic conjunctivitis is an important differential point between inhalants and foods causing a continuation of symptoms, it being present with the inhalants.

Titration does not give one all the answers to the problem of correct dosage, but it comes nearer to doing this than any other one procedure. It is the purpose of this method of testing to give one the best beginning dose, not to establish what the maximum optimum dose will be.

This method of testing, accurately applied, enables a physician to start treatment and accomplish results with patients having symptoms in season and to do so without danger of causing reactions. I have not had one single case of reaction from coseasonal testing with the method outlined here during the past eight years.

Finally, the average best multiple in any area may differ from what has proven to be best in my locale. Therefore, each user must ascertain his own optimum multiple for specific therapy in his geographical area.

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THE TOPICAL APPLICATION OF THEPHORIN
A Study of the Frequency of Eczematous Sensitization

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SINCE Forneau[2] and his French associates developed the first of the so-called antihistaminics or histamine antagonists, numerous compounds have been evolved which have a clinical effectiveness without prohibitive side effects. The fact that the oral administration of these medications is of value in the treatment of allergic dermatoses led to the hope that their topical application might be of additional help. Within the past few years there have been innumerable articles dealing with the subject, and it is not within the scope of this paper to review them. As is well known, there are several antihistaminic agents available for topical application.

Thephorin, the drug used in this investigation, differs chemically from the ethylenediamine derivatives (Antergan, Neo-Antergan, and Pyribenzamine) and the closely related diphenylhydramine compounds (Benadryl and Hydrallin). Thephorin base is a brand of phenindamine which is a polycyclicamine. The oral forms of the drug, syrup and tablet, contain the hydrogen tartrate salt of the Thephorin base which is also used in the ointment. The formula for the Thephorin base is 2-methyl-9 phenyltetrahydro-1-pyridindene. In this study an attempt was made to determine the incidence of eczematous sensitization in patients who had used Thephorin ointment for varying periods of time.

Wooldridge and Joseph[10] (August, 1948) reported the results of the use of Thephorin in the treatment of disseminated neurodermatitis. Their patients were treated with the syrup and tablets orally in addition to the topical use of 5 per cent Thephorin in a carbowax vehicle. Twenty-one patients were treated with both local and oral medications, and two patients received only the ointment. The period of treatment varied from one to seven weeks. Only one of the twenty-three patients became worse, although in this instance patch tests were negative.

Laymon and Schmid[4] (November-December, 1948) investigated changes in the subjective and objective signs in common dermatoses which could be obtained by the application of 5 per cent Thephorin incorporated in carbowax 1500.* Sixty per cent of the fifty-eight cases which were treated with Thephorin ointment were circumscribed neurodermatitis. The duration of treatment varied from three days to three months. Forty-four per cent were treated one week or less; an additional 21.5 per cent, from one to two weeks, and 34.5 per cent, from periods varying from two to twelve weeks. Approximately 12 per cent of the eruptions

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*Supplied by Dr. M. J. Schiffrin of Hoffmann-LaRoche, Inc., Nutley, New Jersey.

became worse following the use of the ointment. In only one patient, however, whose eruption flared following the use of Thephorin ointment, was a patch test performed, which was negative at forty-eight hours. Thus in this group of thirty-four patients eczematous sensitization could be suspected in about 12 per cent, although it was not proved because no patch tests were performed.

There were nine patients with disseminated neurodermatitis (atopic dermatitis). Forty-four per cent of them were objectively worse following the use of the ointment. One patient obtained symptomatic relief for one month, following which she flared and presented a positive patch test to the preparation. No other patch tests were done.

The next group was made up of seven patients who presented eczematous eruptions which could not be classified. None of them became worse following the application of Thephorin ointment, and no patch tests were performed. The Thephorin ointment was also used topically in a group of miscellaneous dermatoses, including two cases of lichen planus, one of psoriasis, one of stasis dermatitis, one of dermatophytosis of the feet and ankles, one of generalized idiopathic pruritus and one of erythematosquamous seborrheic dermatitis of the ear canals. The latter patient obtained temporary objective and subjective improvement but flared six weeks after she had been using the ointment. A positive patch test was obtained. These observations proved that the topical use of Thephorin produced eczematous sensitization in two of fifty-eight patients (approximately 3 per cent). However, since patch tests were not performed in all patients whose eruptions flared, the frequency of eczematous sensitization could theoretically have been much higher.

Madden[6] also attempted to evaluate Thephorin ointment for the relief of itching in 141 cases of varied cutaneous disorders. In this study the cases were selected, and only those eruptions were chosen where it was thought proper to use an ointment. The lesions were generally dry. Vesicular, pustular, secondarily infected or weeping eruptions or those accompanied by cellulitis, lymphangitis, acute lymphadenitis or fever were excluded. In seven cases (5 per cent) the eruptions were aggravated, although no patch tests were performed. For this reason it is impossible to judge the incidence of eczematous sensitization, although one may assume that it was not greater than 5 per cent.

Shelmire[7] (November, 1948) observed six instances of contact-type sensitization among 455 persons, an incidence of 1.31 per cent. He felt that this was a low sensitizing index, especially if one considered that the ointment was used by large number of patients over a comparatively long period of time and that considerable quantities of the preparation were applied.

Sulzberger and Baer[8] recently stated that it is unfortunate that the usefulness of the antihistaminics is impaired by the paradoxic findings that some of them are not always antiallergic but sometimes even rela-

tively strong sensitizers. These authors mentioned that they had seen allergic eczematous contact-type dermatitis from several antihistaminics, including Thephorin and Pyribenzamine, as well as drug eruptions of various kinds from most members of the so-called antihistaminic series.

TABLE I

Types of Dermatoses	No. of Patients	Per Cent
Pruritus (anal and vulvar)	34	10.48
Neurodermatitis (circumscribed)	97	29.92
Lupus erythematosus (chronic discoid)	1	0.30
Dermatophytosis	4	1.23
Contact dermatitis	35	10.80
Atopic dermatitis	24	7.42
Dermatitis unclassified	6	1.85
Pruritus senile	29	8.96
Psoriasis vulgaris	14	4.32
Bites, insect	10	3.08
Tinea glabrosa	1	0.30
Seborrheic dermatitis	16	4.94
Stasis dermatitis	4	1.23
Urticaria	5	1.58
Lichen planus	5	1.58
Dermatitis medicamentosa	1	0.30
Lichen sclerosus et atrophicus	1	0.30
Pityriasis rosea	18	5.56
Dermatitis herpetiformis	2	0.62
Dermatitis solare (acute sunburn)	2	0.62
Pruritus hiemalis	11	3.39
Rosacea	1	0.30
Folliculitis	2	0.62
Herpes zoster	1	0.30
Total	324	100.0

TABLE II

Duration of treatment	No. of patients	Per cent
Up to 7 days	53	16.25
1 to 2 weeks	122	37.75
2 to 3 weeks	40	12.35
3 to 4 weeks	36	11.11
1 to 2 months	37	11.41
2 to 3 months	20	6.18
3 to 4 months	5	1.58
4 to 5 months	4	1.23
5 to 6 months	2	0.62
6 to 7 months	1	0.30
7 to 8 months	2	0.62
8 to 9 months	1	0.30
10 months	1	0.30
Total	324	100.0

PRESENT STUDY

In this investigation, patch tests were performed on 324 patients with various dermatoses who had used Thephorin ointment for periods ranging from a week to ten months. In most of the patients three patch tests were performed, utilizing: (1) the 5 per cent standard Thephorin ointment, (2) carbowax 1500, and (3) a 2 per cent solution of the Thephorin base. The tests were removed at twenty-fours and read at forty-eight hours. The results can be best summarized in tabular form.

There were many patients whose eruptions were aggravated by the use of Thephorin ointment but in whom eczematous sensitization could not be proved by patch testing. In these patients the lesions might have flared if anything or nothing had been used. Table III summarizes those patients whose eruptions were aggravated by the use of the ointment and who

TABLE III

Sex	Age	Diagnosis	Duration of Treatment	Results of Patch Tests
1.F	41	Neurodermatitis	1 month	Ointment-positive Base-0 Solution-positive
2.M	56	Contact dermatitis	2 days	Ointment-3 + Base-0 Solution-4 +
3.F	35	Pruritus vulvae	2 weeks	Ointment-? Base-positive Solution-positive
4.F	50	Atopic dermatitis	2 months	Ointment-3 + Base-0 Solution-4 +
5.F	65	Neurodermatitis	2 weeks	Ointment-4 + Base-Not tested Solution-4 +
There were two other cases in which reactions occurred apparently as a result of sensitization to carbowax:				
1.F	33	Pruritus Ani	8 days	Ointment-positive Base-Not tested Solution-negative
2.F	36	Neurodermatitis	3½ months	Ointment-positive (erythema) Base-positive (erythema) Solution-negative

developed true eczematous sensitization as indicated by a positive patch test.

COMMENT

It would seem from an analysis of these reactions that the time element is of some importance as far as eczematous sensitization to Thephorin is concerned. All cases of sensitization developed within a period of two months, and none of the sixty-three patients who continued the use of the preparation longer than two months encountered any difficulty. It is noteworthy that every single instance of sensitization occurred in patients who had eczematous eruptions and that patients with non-eczematous eruptions such as psoriasis, lichen planus, pityriasis rosea, et cetera, encountered no difficulty whatsoever. As is well known, this holds true for sensitizations to innumerable other substances, including the sulfonamides, antibiotics, furacin and other chemicals.

As mentioned earlier, the clinical flare of an eruption does not necessarily mean the development of true eczematous sensitization. Such is the case in all types of topical therapy regardless of the agent which is being used. In this group of 324 cases, eczematous sensitization developed in approximately 1.5 per cent within a period of two months. This indicates that Thephorin is a much less potent sensitizer than several other topical medications such as the sulfonamides, penicillin and furacin. Hopkins and Lawrence,[3] for example, found that allergic cutaneous reactions appeared in 11 per cent of all patients and in 25 per cent of those with eczematous dermatitis who received penicillin topically. Sulzberger, Kanof, Baer, and Lowenberg[9] found that 19 per cent of a group of 254 experimental subjects developed dermatitis following application of the sulfonamides. Downing, Hanson and Lamb[1] noted that approximately 10 per cent of sixty-five patients treated with furacin ointment became

sensitized, while Lynch[5] noted even a higher percentage of eczematous sensitizations (15 to 25 per cent). As time goes on, and Thephorin ointment continues to be used, the percentage of sensitizations may change. While our data on 324 cases indicate that Thephorin ointment sensitizes only 1.5 per cent of individuals upon which it is used, time alone will determine its true index of sensitization.

SUMMARY

1. Patch tests were performed on 324 patients with various dermatoses who had used Thephorin ointment for periods varying from a few days to ten months.

2. Flares of the eruptions plus positive patch tests indicated eczematous sensitization in 1.5 per cent of the subjects.

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INHALANT ALLERGY

(Continued from Page 630)

tests (or scratch tests under certain conditions) is to be certain as to the relation of any test with a given solution to the entire reaction. Specifically, one must be sure that a certain response, considered significant, is either the end point of reaction or has a definite relationship to it. In a subsequent communication these points will be discussed in detail.

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CORN SUGAR AS AN ALLERGEN

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RINKEL first called attention to the clinical significance of corn sensitivity, having demonstrated in an exhibit at the annual meeting of the Southern Medical Association in 1936 that corn was fourth among various foods listed in the order of the incidence of sensitivity. Since that time he has continued to emphasize the importance of sensitivity to maize and its products, finally presenting the problems of the corn-sensitive patient at the Omaha Instructional Course of the American Academy of Allergy in 1947.

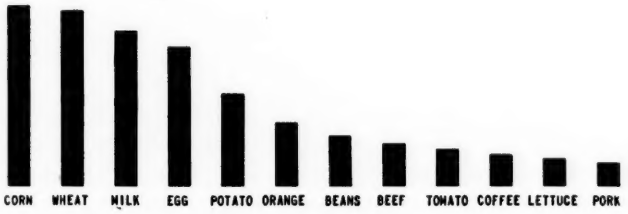

Fig. 1. The order of incidence of foods causing masked or cumulative allergic reactions. The incidence of sensitivity to corn, wheat, milk and eggs was determined from a survey of 200 consecutive cases studied for food allergy by direct methods, i.e., by means of individual food tests with those four foods and subsequent clinical follow-up. The relative incidence of sensitivity to other foods is estimated from clinical experience.

One of us (T.G.R.), in discussing another paper on the subject of food allergy at the 1946 annual meeting of the American Academy of Allergy, stated that corn sensitivity was second only to wheat as a specific cause of chronic food allergy. This statement was based on a study of eighty-five consecutive cases investigated for the presence of specific food sensitivity by means of individual food tests with wheat, corn, milk and eggs. This series has since been extended to include 200 consecutive cases studied similarly, the results of which indicate that corn sensitivity is now at least equal to that of wheat allergy and appears to be slightly greater in incidence, as illustrated in Figure 1. This study, comprising 160 adults and forty children of pediatric age, has been reported elsewhere.[5,10]

Urbach and Willheim[21] suggested the possibility of allergic reactions to sugar of corn origin in 1932. Rinkel has repeatedly stressed the importance of corn sugar in respect to handling the corn-sensitive patient for over a decade, presenting a case at the first instructional course of the American College of Allergists in 1944, which illustrated that the inges-

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tion of corn sugar in bacon caused headaches,[16] and that corn sugar in candy, gum, ices, commercially canned fruit and pharmaceutical preparations resulted in allergic reactions in individuals sensitive to corn. Coca[1] also referred to the fact that an individual sensitive to corn must avoid corn sugar. The first comprehensive experimental study of this problem was made by Ratner and Gruehl[11] in 1935. They determined that corn sugar syrup and crystalline sugar, derived from the hydrolysis of corn starch, were non-anaphylactogenic for guinea pigs, and, presumably from this data, concluded that these products were not important in clinical allergy. At least, other evidence, such as experimental feeding tests with corn products or even skin tests with extracts of corn, was not cited in reaching this conclusion.

Although we have been able to confirm their anaphylactic studies in guinea pigs, we are not in agreement with their deductions regarding the clinical significance of corn sensitivity. This presentation will deal, primarily, with the clinical evidence in support of the thesis that sugars of corn origin are allergenic in many highly corn-sensitive individuals.

It should be pointed out at the onset that our opinion on the subject of corn sensitivity has undergone considerable change during the course of the past five years. Interest in the detection of clinical allergic reactions to corn has developed as we gradually learned the sources of corn in the diet and thus became able to instruct our patients more adequately in its specific avoidance. We were aided in the beginning by having access to the list of corn sources compiled over a previous period of several years by Rinkel.[12] However, we were still unable to relieve completely the symptoms of certain cases of corn sensitivity, even though they were correctly diagnosed in this respect, until we had learned of the presence of corn starch employed as a sizing on the inner surface of paper food containers,[6] of the commercial practice of dusting the surfaces of certain plastic-type containers with corn starch,[6] of the use of corn starch as a diluent and excipient in many pharmaceutical preparations,[7] and of additional sources of corn sugar in other prepared foods and medications. In this connection it might be added that we have never observed a patient, even though he knows that he is corn sensitive and has attempted to avoid its ingestion, who has been able to remove corn from his diet in the absence of specific instructions of *how* to do so.

The other major factor in our ability to recognize the clinical significance of this problem occurred coincidentally with the abandonment of the practice of performing skin tests with food extracts five years ago, since which time the individual food test has been employed as the major diagnostic criterion for the detection of specific food sensitivity. The present technique of this test, described by Rinkel,[14] has been confirmed by Randolph and Rawling.[9]

In an attempt to appraise the clinical importance of this question, one of us (T.G.R.) in 1944 subjected all new patients suspected of having symp-

toms due to food allergy to the deliberate experimental feeding of corn. The results of this study were impressive in respect to the true incidence of corn allergy. Since this time, all new patients and many previously studied, who had symptoms of the general type suggestive of food sensitivity, have been subjected routinely to individual food tests to determine the existence of allergy to corn.

From this experience, it is our impression that current differences of opinion in respect to the clinical significance of allergy to maize and its products is due in part to the inability of patients and clinicians to avoid its ingestion, and in part to the perpetuation of out-moded methods of specific food diagnosis. In the latter connection, we refer particularly to the mechanical performance of cutaneous and intracutaneous skin tests with food extracts and, to a lesser extent, to the continued use of certain restricted diagnostic diets which do not specifically eliminate certain corn-containing products.

In order to prepare a patient adequately for an individual food test with corn, it is essential that *all* ingested sources of corn be completely avoided for at least four days prior to experimental feeding; otherwise the masked symptoms of corn sensitivity may be perpetuated, and under such circumstances an experimental feeding may fail to produce a diagnostic clinical response. Furthermore, in keeping with the fundamental concept of masked food sensitivity developed by Rinkel,[13] the patient being tested in the absence of adequate preparation might be expected to have his chronic smoldering symptoms actually improved following a meal of corn. A case may be cited to illustrate this common error in the specific diagnosis of corn allergy:

Case 1.—M. M., a man, aged thirty-nine, had been subject to perennial allergic rhinitis and severe chronic headaches, associated with some of the symptoms of the fatigue syndrome, as originally described by Rowe[18,19,20] and recently reviewed.[3,4] An individual food test with milk was associated with the prompt development of severe headache and somnolence. When interviewed, following his test with corn, he volunteered the information that he knew that this food was not causing trouble because he felt decidedly better after eating the test-feeding than he had immediately prior to it. This type of remark, to one familiar with the method, arouses the suspicion that his preparation for the test may have been faulty. It then developed that he had been in the practice of eating a brand of bacon cured by means of a process known to have contained corn sugar and had received his last feeding of this in the morning prior to his noon test for corn sensitivity. He was then told to follow his instructions adequately (the highly corn-sensitive patient must eat only certain approved brands of bacon to be certain that all sources of corn are removed) in preparation for a second test. With this he promptly developed reactive symptoms of a severity and time sequence diagnostic of specific allergy.

The following cases will be cited to illustrate the necessity for the continued avoidance of corn sugar in order to effect relief of symptoms due to corn sensitivity:

Case 2.—L. C., a woman aged forty-eight, had been subject to the typical symptoms of the fatigue syndrome for the past seven years. In her case, these included unexplained fatigue, depression, melancholia, irritability, tachycardia, intermittent chilliness and generalized muscle aching. She had also complained of chronic soreness of her throat, postnasal discharge and intense itching of the eyelids and ear canals. Her individual food test with corn was associated with generalized abdominal discomfort, followed by acute abdominal cramps and diarrhea, with delayed symptoms during the night of the test consisting of insomnia, generalized pruritus and urticaria. The elimination of corn and other incriminated foods resulted in a striking improvement of her local and constitutional symptoms. She returned six weeks later, stating that she had had a return of her weakness and aching for the past four days. The food diary revealed that she had eaten tenderized ham in the evening meal prior to the onset of these symptoms and had also consumed it in two subsequent additional feedings immediately prior to the recurrence of her depression and melancholia. Upon inquiry, the statement of the manufacturer revealed that this brand of ham contained corn sugar. Her symptoms subsided with the omission of ham but recurred subsequently following its reintroduction to the diet. Follow-up observations revealed that she tolerated fresh pork and other recommended brands of ham which were processed without the addition of corn sugar.

Case 3.—J. R., aged four, had complained for several months of chronic coughing, recurrent "colds" and gastrointestinal symptoms which on several occasions had suggested the possibility of intestinal obstruction. Her father, a physician, had been particularly concerned with her chronic listlessness, irritability and sluggishness, more marked on certain days than on others. He had noticed that she was developing into a progressively troublesome behavior problem, meeting a characteristic description.[4]

She was found to be highly sensitive to house dust, wheat, corn and egg. With the continuation of specific dust therapy and the elimination of these foods, there has been a striking improvement in her symptoms and general behavior. For the last year she has remained an active, healthy and well-adjusted child. Coincident with starting nursery school, however, she lapsed into her former symptoms. It was then learned that the fruit juices served during mid-morning at the school were sweetened with corn sugar. Her symptoms again subsided with the cessation of these drinks and recurred when they were returned to her diet, although she was not clinically sensitive to any of the fruits as such. On another occasion similar symptoms were reproduced when she was served maple syrup, subsequently learned to have been adulterated with corn syrup.

Several acute allergic reactions have been observed to follow the ingestion of various types of corn sugar; illustrative examples are given in the following cases:

Case 4.—E. M., a physician's wife, aged twenty-two, gave a history of intermittent asthma since childhood, acute gastrointestinal upsets beginning at the age of fifteen and the onset of perennial allergic rhinitis and chronic fatigue at the age of nineteen. Her fatigue and weakness were accentuated intermittently in association with periods of tender, swollen cervical glands, as previously described,[8] and particularly with bouts of acute rhinitis occurring in the middle and late summer months prior to her first visit in May, 1946.

Specific treatment for her house dust sensitivity failed to afford satisfactory relief of her symptoms. Food diary evidence revealed attacks of sneezing, pruritus and urticaria following meals containing corn on the cob. An individual food test

with corn (using corn meal gruel only) was followed by abdominal cramps, generalized itching, marked fatigue and a recurrence of her tender, swollen, anterior cervical lymph glands. The complete elimination of corn products and the continuation of dust therapy afforded complete relief of symptoms.

After several weeks of corn avoidance, she reported an inexplicable attack of severe sneezing and nasal obstruction which started during the evening meal and continued all night. She was slightly nauseated the following morning and remained exceedingly tired throughout that day. She was at a loss to explain this attack because she had not eaten any food previously known to have caused symptoms. Neither were there any clues in her food diary to explain this acute reaction. After a prolonged period of questioning, it finally came out that corn on the cob had been served to other members of the family and that it had been cooked by the patient. The same meal was repeated five days later and produced an identical type of reaction, but the same menu with the absence of corn was tolerated. Subsequently it has been shown on repeated occasions that the inhalation of the fumes of cooking corn (osmyls) will produce acute allergic reactions in this individual.

Early in the course of this patient's studies, an attempt was made to determine the effect of the ingestion of dextrose. On the fifth day following an acute corn reaction, this food having been absolutely eliminated in the interim, she was fed 150 grams of U.S.P. dextrose (C.P.), dissolved in 300 c.c. of tap water. Within five minutes she drank an additional 200 c.c. of water. Fifteen minutes later she developed nausea and complained of feeling tense and "shaky," and at thirty minutes she first noticed abdominal cramps. An hour after the first dose, an additional fifty grams of dextrose was administered in 150 c.c. of water. Her nausea was accentuated within ten minutes, followed by vomiting at twenty minutes. One hour after the second feeding she developed mild rhinitis and sneezing, which persisted for a half hour, and a severe frontal headache which remained troublesome for three hours. She remained unusually tired for the following day, during which time she continued to have occasional abdominal cramps.

The question may be raised, which cannot be denied, that the amount of glucose ingested would have made any person sick. It should be pointed out, however, that the amount of the first dose was approximately that given in routine glucose tolerance tests and that she developed symptoms prior to the second feeding. Furthermore, the symptomatology which she exhibited is typical of that of the allergy patient and identical symptoms have been produced in her following the ingestion of other forms of corn.

During the past two years this patient has been very helpful in her ability to detect the presence of corn sugar in unlabeled processed foods. For instance, she has been able to determine its presence in certain brands of canned fruits and vegetables, a particular brand of Graham crackers, waffle syrup (alleged to have been maple but subsequently found to have been adulterated with corn syrup) and other prepared foods not suspected of containing corn at the time they were eaten. It is from patients of this type and degree of sensitivity that we have been able to determine the sources of corn in the diet.

Case 5.—M. McW., aged thirty-seven, had been subject to severe perennial allergic rhinitis with intermittent complete nasal obstruction and marked itching of her nose for five years, and frequent headaches and occasional urticaria for a year prior to her first visit. Tomatoes were suspected of causing hives, but no other foods were under suspicion except corn, which caused gastrointestinal distress, presumably on the basis of its "roughage."

House dust hyposensitization resulted in only partial improvement of her rhinitis. There was no other evidence of inhalant sensitivity.

Sixty cubic centimeters of corn syrup (stated by the manufacturer to be free of

all other agents except corn syrup) were ingested, while fasting, at a time when the patient was symptom-free after four days of complete corn avoidance. She developed a blinding headache ten minutes later, followed immediately by marked dizziness. The patient was obviously acutely ill and too dizzy to walk across the floor. She was helped to her feet but was unable to stand with her eyes closed in attempting to perform a Romberg test. She was aided in returning to her home. Dizziness, headache and extreme fatigue persisted for two days.

She was also found clinically hypersensitive to wheat and onion. With the continuation of dust avoidance and specific therapy and the complete elimination of corn and other incompatible foods, she has had complete relief of symptoms during the past two years except when she would inadvertently encounter sources of corn. On repeated occasions the ingestion of corn syrup or corn sugar (dextrose or glucose) would be followed by the recurrence of allergic symptoms.

Case 6.—M. F., assistant hospital superintendent of nurses, aged thirty-seven, had been subject to typical atopic dermatitis until the age of twenty-seven, intermittent bronchial asthma and perennial allergic rhinitis for five years, and periodic frontal headaches associated with extreme fatigue since childhood. In the year prior to her first visit in July, 1945, she had complained of increasing frequency and severity of headaches which were associated with continuous fatigue. Acute indigestion with heartburn and bloating occurred after certain meals. Chicken was suspected of causing this reaction, but it only accounted for a few of her attacks.

There was no history or skin test evidence of inhalant sensitivity. An individual food test with canned corn was followed by tenseness and "nervousness" at forty-five minutes. A second feeding an hour later was followed by a severe headache, dizziness and mental confusion. Residual fatigue persisted for twenty-four hours.

Five days later, a clinical test with corn syrup was performed. She had completely avoided corn and other known allergens for four days prior to the test, and was symptom-free and fasting when fed 60 c.c. of Karo syrup with as much water as desired. Forty minutes later she complained of drowsiness but developed no other symptoms. She was fed half the amount an hour after the first dose. Ten minutes later she noticed an increase in her somnolence associated with the desire to sneeze; these symptoms continued for the remainder of the day, and three hours after the last feeding, they became associated with increasing nausea. Four and one-half hours after the second feeding she complained of marked weakness, trembling and shaking. Seven hours after the second feeding (having had no other foods or medications in the interval) she developed severe generalized abdominal tenderness, distention and cramps, followed by acute nausea. Shortly thereafter she passed a liquid stool which was followed in the next five hours by eight to ten additional diarrheic stools, which contained much mucus, the last three containing fresh blood. Severe nausea and griping abdominal pains persisted through the night. The following morning she felt better except for extreme fatigue. However, at 8:00 p.m. the second day she developed chills and a temperature elevation of 101° F., followed immediately by a severe attack of asthma which necessitated her admission to the hospital. All food ingested since her corn test and prior to her asthma had been shown to be compatible as a result of subsequent observation. There was no other apparent cause of the clinical reaction described except the ingestion of corn syrup.

She was also shown to be clinically sensitive to chicken, peas, and milk. With the avoidance of these foods and all sources of corn, she had no further troublesome symptoms. A year later she developed a minimal tuberculous lesion of the chest but otherwise has enjoyed the best of health except when encountering sources of corn or other incriminated foods.

TABLE I. UNSUCCESSFUL ATTEMPTS TO PRODUCE ACUTE ANAPHYLAXIS BY THE INTRAVENOUS ADMINISTRATION OF CORN SYRUP IN GUINEA PIGS IN WHICH PREVIOUS EFFORTS HAD BEEN MADE TO INDUCE CORN SENSITIVITY

	Sensitizing Procedure					Shocking Procedure			
Material Used:	A. 50% Aqueous Solution of Corn Syrup B. Saturated Solution of Corn Flour C. Corn Flour in Aluminum Hydroxide Cream					1.0 cc. 50% Aqueous Solution of Corn Syrup Injected intravenously in all cases.			
Route of Sensitizing Doses	No. of Guinea Pigs	No. of Injections	Interval in Days Between Doses	Amount Injected in cc..	Material Injected	Interval in Days After Last Injection	Acute Anaphylaxis	Questionable Anaphylactic symptoms	No Symptoms
Intraperitoneal	2	2	4	5.0	A.	19	—	—	2
	6	3	3	5.0	A.	16	—	—	4
	2	2	6	1.0	B.	16	—	—	2
Subcutaneous	2	3	3	2.0	A.	14	—	1	1
	2	1	—	1.0	B.	14	—	—	2
	3	2	6	1.0	B.	16	—	1	2
Intramuscular	4	1	—	1.0	C.	16	—	1	3
	4	2	7	1.0	C.	23	—	1	3

These patients, as well as many others observed in our practice, have been able to detect exceedingly small amounts of corn sugar or syrup as it is encountered in commercial foods. In numerous instances we first became aware that certain foods produced symptoms in our controlled corn-sensitive patients, and then determined from correspondence with the manufacturer that the foods in question actually did contain sugar of corn origin.

Other cases of corn sensitivity in children in which the accidental or intentional ingestion of corn sugar produced acute allergic symptoms have recently been reported by one of us.[4]

In view of the statement of Ratner and Gruehl[11] that corn sugar syrup and crystalline sugar derived from corn were non-anaphylactic for guinea pigs, attempts were made to sensitize twenty-five guinea pigs to various corn products, following which an intravenous injection of corn syrup was administered in an effort to produce anaphylaxis. The following materials were used as antigens: 50 per cent corn syrup in aqueous solution (ten pigs), a saturated solution of corn flour in saline (seven pigs), and corn flour suspended in aluminum hydroxide cream prepared by the method of Hektoen and Welker[2] (eight pigs). The corn syrup used in the experiments was furnished by the Corn Products Refining Company. According to their analysis, the dextrose equivalent of the undiluted syrup was between 42.5 and 44.5, the remainder of the material consisting of dextrins. The sample contained 0.037 per cent total protein, and no ammonia nitrogen was found. The varying dosages and the routes of administration of the sensitizing injections and results of the experiments are summarized in Table I.

As may be observed from this table, we were unable to induce acute

anaphylaxis in any of the test animals. The term "questionable" anaphylactic symptoms refers to rubbing of the nose and sneezing. One animal, injected intraperitoneally by repeated doses of corn syrup, developed fecal incontinence in addition. All "reactions" were transitory, and it cannot be said that they constituted true anaphylactic responses.

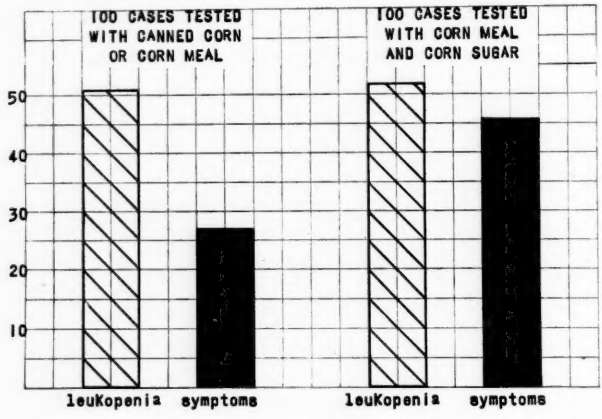

Fig. 2. The incidence of corn sensitivity as determined by individual food tests.

DISCUSSION

In view of the frequency with which acute reactions may be produced in corn-sensitive patients, following the experimental or accidental ingestion of sugar of corn origin, the reader may wonder why the allergenicity of corn sugar has not received greater emphasis. Perhaps Ratner and Gruehl's observations that corn sugar did not act as an anaphylactogen, and presumably not as an allergen, retarded the clinical recognition of the matter. However, the major factors in our failure to appreciate the problems associated with corn allergy appear to be: first, the fact that sensitivity to corn is usually a masked type of clinical response and, therefore, not readily observed either by the patient or his physician; and second, the fact that corn products are so widespread in the diet that it is difficult to eliminate them completely so as to effect clinical relief.

Rinkel[13] has shown that a patient will recover from the masked effects of a food taken frequently in the diet after a four-day period of complete avoidance. The experimental ingestion of corn sugar in the highly corn-sensitive patient, who has been receiving corn daily for several weeks before avoiding it prior to such a test, is frequently followed by a sharp and unmistakable clinical reaction.

In fact, the highly sensitive patient, otherwise controlled as far as his corn allergy is concerned, will usually react with more immediate symptoms following the ingestion of corn sugar than he will from eating corn starch,

corn as such, or corn oil. This phenomenon, also observed independently by Rinkel,[12] has been shown to exist in a series of 100 consecutive individual food tests performed by feeding cooked corn meal only, as compared with a similar group of undiagnosed patients suspected of food allergy but fed cooked corn meal plus corn sugar. The striking difference in the frequency of reactive symptoms in relation to the presence of a leukopenia of 10 per cent or greater, occurring from any previous total leukocyte count, is illustrated in Figure 2. The addition of corn sugar to the test feeding has materially increased the diagnostic accuracy of individual food tests with corn as determined by the production of objective symptoms. There appears to be no appreciable difference in the actual incidence of corn sensitivity in the two groups of cases as determined by the results of cumulative feeding and clinical follow-up. Prior to making this change in our test technique, we were disturbed by the fact that we were not encountering the same percentage of reactive symptoms in our cases of corn sensitivity under test conditions as in the cases of wheat, milk or egg sensitivity. Since making the above change in technique and learning of the additional sources of corn starch—in food containers[6] and as excipients in pharmaceuticals[7]—we have encountered about the same percentage of symptoms in the corn cases, in respect to the definition of leukopenia, as in similar tests with other foods.

In a great many corn-sensitive individuals, the chronic symptoms of corn allergy will not subside until corn sugar has been completely eliminated. This entails the avoidance not only of corn syrup but also of dextrose, glucose (including such trade name products as Cerelose, Sweetose, Dyno, Cartose, Karo and Puretose), a problem that has been rendered even more difficult by inadequate federal labeling regulations. Actually, corn sugar is used so widely in commercially sweetened products that the consumer must assume that the current designation of "sugar" may mean sugar of corn origin. At the present time, in order to avoid corn exposure, the patient must buy only recommended trade name products of certain types of commercially prepared foods. An attempt is now being made to bring a list of this type up to date; this data will be published elsewhere.[17]

The question may be raised concerning the possibility of intravenous dextrose or glucose causing reactions in corn-sensitive individuals. Although the incidence of such reactions is not known, there is no doubt that they occur, as judged by the histories of exquisitely corn-sensitive patients and a few instances where clinical reactions have been experimentally induced following the intravenous administrations of dextrose (unpublished observations). Specific reactions to intravenous dextrose or glucose are more apt to occur in cases of diagnosed corn sensitivity in which corn has been completely eliminated for a short time prior to intravenous therapy. There would appear to be less danger of such reactions when corn and corn products have been continued in the daily diet prior to the administra-

tion of corn sugar intravenously. From preliminary observations it may be said that clinical reactions from intravenous solutions of glucose or dextrose do not occur in all individuals in whom it is possible to precipitate a clinical response from oral feeding of corn sugar. This problem is under current investigation and will be reported subsequently.

Due to the frequency of corn sensitivity, as encountered in clinical allergy, the question should be reopened as to whether the almost universal practice of using corn sugar in infant feeding is a desirable procedure. Corn allergy is an important cause of infantile eczema and gastrointestinal allergic reactions in infants, and of other allergic responses in older children. In view of this and the relative ease with which clinical sensitivity to corn may be induced, it is our belief that corn sugar should at least be rotated with other sugars in infant feeding, as a prophylactic measure in keeping with the recently described observations of Rinkel.[15] If one sugar is to be used exclusively, cane sugar would appear to be preferable, as specific sensitivity to this product is less common. Carbohydrate derived from hydrolyzed tapioca or potato starch might also be used. Beet sugar must be considered as somewhat less desirable because of the relatively greater frequency of beet sensitivity as compared to cane sensitivity and the fact that the ingestion of beet sugar will cause symptoms in certain beet-sensitive patients.

A critical evaluation of the merits or demerits of the current vogue of employing corn syrup and malted corn products as sources of a carbohydrate in infant feeding, as far as it is related to the development of specific allergy, cannot be answered by us, as we see only allergic children. In the children that do come to our attention, corn sensitivity is a major if not the leading current food allergen.

There is no reason to believe that the problem of corn sensitivity is limited to certain geographic regions, in view of the widespread distribution of processed foods and the fact that the incidence of allergy to major foodstuffs is directly proportional to the incidence of specific foods in the diet. However, as adjudged from the eating habits prevalent in areas of the South and by the fact that a relatively higher percentage of native Southerners have been found corn sensitive as compared with a similar group living in the Northern Midwest, it seems probable that corn sensitivity might be more prevalent in that general area.

SUMMARY

Contrary to the generally prevalent impression, corn sensitivity is an exceedingly important clinical problem and ranks with wheat in the incidence of chronic food allergy. Under the proper experimental conditions, the ingestion of corn sugar by the highly corn-sensitive individual is apt to be followed by allergic symptoms.

Corn is, by all means, the most difficult food in the American diet to avoid. The treatment of corn allergy entails the elimination of all sources

of corn; in respect to corn sugar this means the exclusion of dextrose, glucose and commercial brands of corn sugar and syrup.

In view of the high incidence of corn sensitivity, the widespread practice of using corn syrup in infant feeding should be carefully investigated.

We agree with earlier work that corn sugar is not an effective anaphylactogen in guinea pigs.

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THE USE OF BACITRACIN, A NEW ANTIBIOTIC, IN AEROSOL FORM

Preliminary Observations

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THE DISCOVERY of a new, readily available antibiotic always evokes interest in its potentialities and inevitably leads to a comparison with older existing antibiotics. Bacitracin, first reported by Johnson, Anker and Meleney[6] in 1945, has been no exception. This antibiotic, recovered from a strain ("Tracy I") of B. subtilis, is a neutral crystalline powder, water soluble and relatively heat stable (fifteen minutes at 100° C.). It is active *in vitro* chiefly against Gram-positive organisms, both aerobic and anaerobic, and ineffective against Gram-negative organisms, with the exception of the gonococcus and meningococcus. Some fungi and spirochetes[4] are highly susceptible. In these respects bacitracin resembles penicillin. It differs, however, in that bacitracin is poorly absorbed from topical applications, from the gastrointestional tract[2] and from the respiratory system, as will be shown later. This makes it, therefore, a drug of choice wherever local, concentrated antibiotic action is desired. This is especially true since bacitracin is locally nontoxic and nonirritating.[7] It has been recently demonstrated that powdered bacitracin may be applied to the surface of the brain without causing the convulsions which are characteristic of the application of penicillin, streptomycin and the sulfonamides. Moreover, it can be injected into the brain tissue or into the ventricles in a concentration of 1,000 units per c.c. without causing any evidence of irritation.[3]

There is the possibility, though, that bacitracin may have nephrotoxic effects following systemic administration.[8] However, this observation was made with certain lots of bacitracin and may be due to by-products of manufacture, which, it is hoped, will eventually be removed to produce a purer product.

Its use to date, therefore, has been practically confined to the local treatment of various types of surgical infections, pyodermas and ophthalmic infections.

Accordingly, the authors felt that bacitracin in aerosol form should be particularly beneficial in the treatment of sino-respiratory infection, which is primarily a local condition. The following additional advantages possessed by bacitracin tended to strengthen this belief:

1. It is relatively nonsensitizing as compared with penicillin.[8]
2. It can be used where penicillin hypersensitivity exists.

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3. It is not inhibited by tissues, secretions, or organisms which produce penicillinase and is, therefore, effective even in mixed infections.[7]

4. It apparently does not cause the production of any specific inhibitory enzyme, such as bacitracinase.

5. It appears to act synergistically with penicillin.[4]

6. It is not destroyed to any extent by propylene glycol, the vehicle employed in this study.[14]

This investigation was undertaken, therefore, to determine the value of bacitracin in aerosol form in the treatment of sino-respiratory infection.

MATERIAL AND METHODS

The bacitracin was dissolved in propylene glycol, which was the vehicle of choice primarily due to its ability to produce long-sustained aerosols. Furthermore, aqueous solutions were not practical due to the marked foaming induced by the detergent property of bacitracin. Besides, it was believed that propylene glycol had the following additional advantages: (1) unusual solvent properties that may possibly affect its penetration into mucous membranes as it does into skin; (2) the slight inhibitory action that it has in blood serum against some organisms.[9]

In order to accelerate solubility, the bacitracin was first dissolved in 2 to 3 c.c. of water and then the propylene glycol was added to make 20 c.c. This was always freshly prepared just prior to treatment. The dose of bacitracin varied from 12,000 units to 134,000 units, administered daily, most patients receiving 40,000 units. Patients were treated from four to twenty-four days. Where combined aerosols were employed, soluble crystalline penicillin G tablets in 100,000 unit dosage and in some cases, where indicated, streptomycin-calcium chloride complex, 0.5 gm. or 1.0 gm., were added. Treatment was continued whenever possible for one week after nasal secretions and/or sputum became nonpurulent in appearance. Results were recorded as "slight," "moderate," or "marked improvement"; "unimproved," or "worse." These were based on the degree of subjective improvement plus the improvement in physical signs, and the partial or complete clearing of nasal secretions and sputum.

Where nasal obstruction existed due to mucosal edema, a nasal decongestant was used preliminary to aerosol treatment. In patients with asthma, whenever necessary, an antispasmodic like aminophylline or Isuprel, singlely or in combination, by open inhalation was administered first in order to enhance the utilization of the antibiotic administered subsequently.[10]

The bacitracin was aerosolized by a combined steam generator and aerosolizer, and administered to the patient through a breathing box, thereby confining and conserving the aerosol, and in this way assuring the patient the maximum utilization of the antibiotic.[11] Besides, bacitracin given by the open method has a disagreeable odor and taste which are almost entirely eliminated in a closed system such as the breathing box. Infants and very small children were treated in a tent.[11]

TYPES OF CASES TREATED

As allergists, the authors recognized the existence of various extrinsic and psychogenic factors in many of the allergic patients, but only those with sino-respiratory infection were studied. This infection was either the sole cause of the patient's symptoms or complicated existing extrinsic allergic or psychogenic factors.

A total of 112 patients suffering with various types of sino-respiratory infections were treated. All of these were ambulatory patients from the private practices of the authors, except for four children treated on the pediatric ward of the Flower-Fifth Avenue Hospital. The conditions treated included acute and chronic paranasal sinusitis, acute and chronic bronchitis, bronchiectasis and infective asthma. These occurred either singly or in various combinations. The ages of patients ranged from twelve months to seventy-four years, and the duration of the condition treated varied from several days to about fifty years. Most of the patients had previously been treated elsewhere by the methods commonly used in allergic practice, and some had already been treated with penicillin aerosol.

All patients were given a complete physical examination, with emphasis on the sino-respiratory tract. Special attention was paid to the appearance of the nasal mucosa, the presence of nasal polyps, and the amount and character of the nasal secretions. In the bronchitic, bronchiectatic and asthmatic patient, the amount and character of the sputum were noted.

With few exceptions, x-rays were taken of the paranasal sinuses or chest, or both. Urinalysis was done every other day in selected cases, especially those receiving larger doses of bacitracin. This was deemed advisable in order to ascertain whether or not the bacitracin was exerting any nephrotoxic action. In a group of selected cases, bacteriologic studies including bacterial sensitivity to the antibiotics were made with organisms cultured from the throat and, in some cases, from the sputum or nose. Absorption studies for bacitracin were limited to eight cases and will be presented later.

RESULTS

To simplify analysis, the conditions treated were divided into "paranasal sinus infection," "respiratory infection," including bronchitis, bronchiectasis and infective asthma, and "sino-respiratory infection," a combination of the two.

A total of 112 patients were treated. Of these, only 100 are reported here due to insufficient data on the remaining twelve cases. Of these 100 cases, seventeen were treated with bacitracin alone, the remaining eighty-three receiving the combined bacitracin-penicillin aerosol. The results following treatment are tabulated in Tables I and II.

Although no accurate evaluation can be obtained from such a small series treated with bacitracin only, it is, nevertheless, interesting to ob-

TABLE I. RESULTS OBTAINED BY TREATMENT WITH BACITRACIN AEROSOL OF 17 PATIENTS WITH SINO-RESPIRATORY INFECTION

Type of Infection	No. of Patients	Marked Improvement		Moderate Improvement		Slight Improvement		Unimproved		Worse	
		No.	%	No.	%	No.	%	No.	%	No.	%
Paranasal Sinusitis	8	3	37.5	3	37.5	1	12.5	1	12.5	0	0
Respiratory	1	1	100.0	—	—	—	—	—	—	0	0
Sino-respiratory	8	3	37.5	3	37.5	—	—	2	25.0	0	0
Totals	17	7	41.2	6	35.3	1	5.9	3	17.6	0	0

TABLE II. RESULTS OBTAINED BY TREATMENT WITH COMBINED BACITRACIN AND PENICILLIN AEROSOL, OF 83 PATIENTS WITH SINO-RESPIRATORY INFECTION

Type of Infection	No. of Patients	Marked Improvement		Moderate Improvement		Slight Improvement		Unimproved		Worse	
		No.	%	No.	%	No.	%	No.	%	No.	%
Paranasal Sinusitis	37	21	56.8	7	18.9	4	10.8	5	13.5	0	0
Respiratory	12	8	66.7	3	2.50	—	—	1	8.3	0	0
Sino-respiratory	34	26	76.5	6	17.6	—	—	2	5.9	0	0
Totals	83	55	66.3	16	19.3	4	4.8	8	9.6	0	0

serve in these tables the favorable results (moderate and marked improvement) obtained with bacitracin alone and with combined bacitracin-penicillin—76.5 per cent and 85.6 per cent, respectively, as compared to 73 per cent obtained with penicillin only, on a comparative dosage basis as previously reported.[12]

Table III presents summaries of a selected group of patients treated with bacitracin singly or in combination. These were chosen to illustrate the type of case treated and the indications for the use of bacitracin. These included previously treated patients who were considered as failures with penicillin aerosol, and instances of sensitivity to penicillin. Patients were improved for a period lasting from two weeks to about one year. This factor depended, in many instances, upon the frequency of common colds, which either served to flare up a mild, subclinical focus or produce a new infection.

BACTERIOLOGIC STUDIES

In order to evaluate the result of specific antibiotic therapy, it is desirable to know the identity of the organisms and their responsiveness to the antibiotic by *in vitro* testing (sensitivity tests). This was undertaken in a number of patients prior to treatment or whenever information was desired, during or after termination of treatment, in order to evaluate the therapeutic agent administered.*

Originally, cultures were taken from the nose and throat and, in some

*Dr. Norman Molomut of the Biologic Laboratories, Brooklyn, N. Y., performed the bacteriological and sensitivity studies.

TABLE III. RESUME OF SELECTED CASES TREATED WITH BACITRACIN AEROSOL — SINGLY OR IN COMBINATION

No.	Patient	Sex	Age	Symptoms and Diagnosis	Duration of Complaint	Culture	Sensitivity Tests	Treatment	Total Dose (x 1000)	Clinical Results	Comment
1	E.F.	F.	59	Asthma Sinusitis Bronchiectasis Diabetes Nasal polyp	1 year			Pen. 100 M/d. 3 weeks Pen. 100 M/2d. Strep. 1 gm.	2100 600 6 gm.	Mod. imp. No further imp.	Prolonged treatment with penicillin gave moderate improvement. Streptomycin ineffective. Bacitracin finally resulted in clearing of infections. No skin testing. No immunotherapy.
						γ Strep.	Pen. 15 u. mod. sens. St. 500 u. resistant	500 M. to 300 M./d	5000	No further imp.	
								Bac. 6000 b.i.d.	252	Marked imp.	
2	R.L.	M.	7	Chr. sinusitis Allergic rhin. Nas. stuffiness Discharge and chronic cough	2 yrs.	Staph. γ Strep. Gm.† Bacilli	Pen. 15 u. resistant St. 500 u. mod. sens.	Bac. 40 M/d.	896	Marked imp.	X-ray: Clouding of left ethmoid and antrum. Previously taken 100 M. penicillin orally for 24 days with no relief. Improvement noted by 2nd week. Remained well for 6 months. No skin testing. No immunotherapy.
3	M.G.	M.	5	Asthmatic bronchitis Sinusitis Laryngitis	5 months			Pen. 100 M/d. 3 weeks	3000	Mod. imp.	Moderate improvement with penicillin by end of 1st week. Complete relief when bacitracin was added. Synergism? Or additional penicillin? No skin testing. No immunotherapy. Well for 1 year.
				Chronic cough	3 years			Pen. 100 M/d. Bac. 20 M/d. 2 weeks	3000 300	Marked imp.	
4	H.G.	M.	18	Ac. sinusitis Nas. stuffiness and P.N.D.	1 week Since infancy			Pen. 200 M/d. Bac. 41 M/d. 11 days	2200 451	Marked imp.	Acute symptoms subsided by 3rd day. Stuffiness and postnasal drip, cleared for first time in years. X-rays taken showed frontal sinusitis, cleared on re-examination after treatment.
5	F.J.	F.	43	Sinusitis Bronchitis Bronchiectasis Asthma Nasal polyp	11 years 3 years	Staph. Strep.	Pen. 15 u. Str. 500 u. resistant	Amin.-Isup. aerosol Pen. 100 M/b.i.d. Bac. 45 M/b.i.d.	2700 810	Marked imp.	Previous treatment with penicillin aerosol in Arizona without relief. Marked improvement with combined therapy. Not completely relieved; organisms resistant to penicillin and streptomycin.
6	E.B.	F.	52	Sinusitis Asthma Psychoneurosis	3 years			Pen. 200 M/d. Bac. 40 M/d.	3500 480	Marked imp.	Previously treated with penicillin aerosol, with excellent results. Pneumonitis with X-ray clearing following combined therapy.
				Pneumonitis	1 week						

7	A.W.	F.	9	Sinusitis (?) Chr. tonsilitis Chronic cough	2 years			Pen. 100 M/d. Bac. 40 M/d.	1100 440	Marked imp.	Tonsils markedly enlarged, obstructive and congested. Scheduled for T. & A. Complete relief of symptoms and marked reduction in size of tonsils.
8	S.S.	F.	19	Mixed asthma (Ragweed pollenosis sinusitis)	2 years			Amin. and Isup. Aerosol Pen. 100 M/d. Bac. 42 M/d.	 2500 250	 Marked imp.	Patient had been taking penicillin aerosol at home—50 M. b.i.d. for 6 weeks (7 million units) without relief. Successful prophylaxis later for a cold. Relieved by combined penicillin and bacitracin. Also given ragweed injections.
9	R.N.	M.	7	Asthma Sinusitis	1 year 5 years			Pen. 100 M } b.i.d. Bac. 40 M }	2300 440	Marked imp.	Status asthmaticus. Previously treated in Baltimore with applications of radon to nasopharynx with temporary relief. Now free of asthma for 6 months. No skin testing. No immunotherapy.
10	G.E.	M.	51	Asthma Sinusitis Bronchitis	1 month 5 years			Amin. and Isup. Aerosol Pen. 100 M } d. Bac. 12 M } Bac. 12 M	 300 36 60	 Moderate imp. Marked imp.	Excellent response to combined aerosol therapy. Developed a rash on face due to penicillin while under treatment. Discarded penicillin, and continued with bacitracin until all infection disappeared. No testing. No immunotherapy. Well for almost 1 year.
11	A.S.	M.	50	Asthma Sinusitis Chronic bronchitis	5 years 10 years			Amin. and Isup. aerosol Pen. 100 M } d. Bac. 40 M } Same w/Strep. 2 days Pen. 300 M/d. and 200 M/d.	 3800 980 2 gm. 2800	Marked but temporary relief Worse Marked imp.	At first good results with penicillin and bacitracin, but had relapse, and when streptomycin was added he was definitely worse. Penicillin in large doses resulted in immediate and marked improvement, which continues. No testing. No immunotherapy.
12	B.O.	M.	42	Chronic sinusitis	15 years	Strep. Staph. Coliform bacilli	All organ. sens. to Pen. Bac. and Strep.	Bac. 67/d	737	Marked imp.	Patient had been previously treated at home with his child in bathroom, in an attempt to eradicate his sinus infection, as well as that of the 5-year old patient. Both did well. Father developed a rash on face. Patch-testing with penicillin was positive. Propylene glycol was negative. Prompt response to bacitracin. Penicillin had previously given 6 months relief.

instances, from the sputum, but this was discontinued since the throat cultures seemed to provide the best information. In several instances, the cultures were grown in media containing the patient's blood, in addition to the routine rabbit's blood media, since it reflected the patient's immunologic response. It was noted in some instances that a hemolytic organism on rabbit blood medium showed no hemolysis with the patient's blood, indicating some degree of immunity; and, conversely, no hemolysis was noted with rabbit blood but was observed on the patient's own blood and, therefore, revealed a lack of immunity and a greater need for antibiotic therapy.

TABLE IV. CLASSIFICATION AND FREQUENCY OF ORGANISMS CULTURED FROM THE THROATS OF 38 PATIENTS PRIOR TO TREATMENT

Organism	Number of times cultured
Streptococci:	
Alpha Hemolytic	5
Beta Hemolytic	13
Gamma (Non-hemolytic)	18
Staphylococci:	
Non-hemolytic	17
Hemolytic (Beta type)	4
N. Catarrhalis	20
Proteus Vulgaris	4
Coliform Bacilli	3
Diphtheroids	3
Pneumococci	1
Tetragenous	1
Hemophilus	1

Table IV lists the organisms identified in thirty-eight patients prior to treatment. Interest centered particularly on the streptococci and staphylococci, in view of their susceptibility to penicillin and bacitracin. The unusual presence of Gram-negative organisms, such as proteus vulgaris and coliform bacilli, was attributed to earlier treatment with penicillin aerosol.

Following the identity of the organisms obtained on culture, they were tested as a combined flora with penicillin, bacitracin, streptomycin and sulfacetimide respectively, to determine their sensitivities. The final concentrations employed in each culture were: penicillin, 1 u./c.c.; bacitracin and streptomycin, 10 u./c.c.; and sulfacetimide, 0.6 mg./c.c.

Inhibitory action was observed at six to eight hour and twenty to twenty-four hour intervals, since it had been noted on occasion that, whereas an inhibiting effect was exhibited for the first six to eight hours, there was a tendency to overcome the antibiotic and have no inhibition in twenty to twenty-four hours. In some cases, this temporary inhibition was noted with only one antibiotic agent, and therefore another one was employed which was more effective. In two instances it was necessary to treat every six hours, day and night, in order to effect complete inhibition. In most instances, however, this was unnecessary, since the inhibition seen during the first eight hours continued through twenty-four hours and enabled us to treat the patient once daily.

Table V records the total number of organisms (ninety) obtained by pharyngeal culture of thirty-one patients prior to treatment, along with the individual sensitivities of each of these organisms to penicillin, baci-

TABLE V. INHIBITORY* ACTION OF PENICILLIN, BACITRACIN AND STREPTOMYCIN AGAINST 90 ORGANISMS OBTAINED BY PHARYNGEAL PRE-TREATMENT CULTURES OF 31 PATIENTS

Number of Organisms:	Number	Per Cent
Obtained by Culture	90	100
Inhibited by Penicillin	64	70.1
Inhibited by Bacitracin	63	70.0
Inhibited by Streptomycin	80	88.8
Inhibited by Penicillin and not others	0	0.0
Inhibited by Bacitracin and not others	1	1.1
Inhibited by Steptomycin and not others	4	4.4
Inhibited by Bacitracin and not Penicillin	9	10.0
Inhibited by Penicillin and not Bacitracin	10	11.1
Equally inhibited by Penicillin and Bacitracin	52	57.6

*Concentration of antibiotics/c.c. in final broth dilution for inhibition studies were:
Penicillin, 1 unit
Bacitracin, 10 units
Streptomycin, 10 units

tracin and streptomycin. The latter showed surprising antibiotic activity (88.8 per cent) in this series, as compared with penicillin (70.1 per cent) and bacitracin (70 per cent). This is probably accounted for by the fact that more than half of these patients (seventeen out of thirty-one) had been subjected to penicillin aerosol therapy previously. This is inferred from the observation of patients who, treated for the first time with penicillin or bacitracin aerosol, ultimately exhibit Gram-negative organisms (coliform bacilli, proteus vulgaris, et cetera) following termination of treatment.

No organisms were observed which were inhibited by penicillin only; one was inihibited only by bacitracin, and nine organisms not inhibited by penicillin were sensitive to bacitracin. Conversely, ten organisms were not inhibited by bacitracin but were definitely sensitive to penicillin. More than half (fifty-two) of the organisms were equally sensitive to penicillin and bacitracin.

Parenthetically, it may be indicated that there were other instances of bacitracin sensitivity not recorded in Table V. Thus in Cases 1, 2 and 5 of Table III there are recorded successful therapeutic results with bacitracin after failure with penicillin and/or streptomycin, and in which cultures and sensitivity tests had indicated poor or no inhibition with penicillin or streptomycin. No bacitracin inhibition tests were performed, and these cases were not included in Table V. Presumably the organisms cultured were inhibited exclusively by bacitracin according to clinical response.

The inhibitory action of the antibiotics as reported in these studies does not, however, take into account the fact that both the bactracin and streptomycin were employed in concentration of 10 u./c.c., in sharp contrast to 1 u./c.c. of penicillin. Different concentrations may have led to different results.

CORRELATION OF CLINICAL RESULTS WITH BACTERIOLOGIC CHANGES

Is there a correlation of clinical results obtained with bacteriologic changes noted following treatment? An attempt was made to answer this question by the observation of seventeen patients (Table VI) in whom

TABLE VI. CORRELATION OF CLINICAL RESULTS AND BACTERIOLOGICAL CHANGES IN 17 PATIENTS TREATED WITH BACITRACIN—SINGLY OR IN COMBINATION

Case	Name	Diagnosis	Pre-Trmt. Culture	Sensitivity Studies†				Treatment	Post-Trmt. Culture	Bacteriologic Changes	Clinical Results
				Pen.	Bac.	Str.	Sul.				
1	Fo.	Asthma Sinusitis	γ strep. Staph P.Vulgaris	+ + −	+ + −	− + +	+ + ±	Pen. Bac. & Strept.	γ strep. Gm-dip. P.Vulgaris	Elim. of staph.	Marked imp.
2	Ti.	Nasal polyp Sinusitis	γ strep. Gm-dip. Staph Gm-bac. (vibrion)	+ + + +	+ + + +	+ + + +	− + + +	Pen. & Bac.	Gm-dip. γ strep. staph.	Vibrion lost	Temp. imp.
3	Me.	Sinusitis	*B strep. *Hemo. staph Gm-dip.	− + −	+ + −	+ + +	− + +	Pen. & Bac.	γ strep. staph. Gm-dip.	Elim. of Hem. staph & strep.	Marked imp.
4	No.	Sinusitis Allergic-rhinitis	γ strep. Staph (hemo.) Gm-dip.	+ + +	+ + +	+ + +	+ + +	Pen. & Bac.	γ strep. Gm-dip.	Staph. elim.	Marked imp.
5	Sh.	Chronic sinusitis	α strep. B. strep. Gm-dip.	± ± ±	± ± ±	± ± ±	− − −	Pen. & Bac.	Gm-dip. γ strep.	α strep. & B. strep. elim. γ strep. appeared	Marked imp.
6	Sk.	Sinusitis Bronchi-ectasis Asthma	B. strep. Staph.	− −	± +	− ±	− −	Bac.	γ strep. staph. B. strep.	None	Worse
7	Myr. S.	Chronic sinusitis	**Hemo. staph γ strep.	+ ±	+ +	+ ±	− −	Bac.	Hemo. staph γ strep. Gm-dip.	No sig. changes	Marked imp.
8	Mck. S.	Acute sinusitis	**Hemo. staph γ strep. Gm-dip.	+ + +	+ + +	+ − +	+ − +	Pen. & Bac.	Hemo. staph γ strep. Gm-dip.	None	Marked imp.
9	Sch.	Acute sinusitis Allergic rhinitis	B. strep. Staph Gm-dip.	+ + +	− + +	+ + +	− − +	P&B & Str.	Gm-dip. γ strep.	B. strep. & staph. elim.	Marked imp.—short duration
10	Sch.	Nas. polyp Sinusitis Allergic rhinitis(?)	γ strep. Gm-dip. Pneumo-cocci. Colif. bac.	+ − − −	+ + + −	+ + + +	+ + − +	Bac.	γ strep. Staph. Gm-dip. Colif. bac.	Pneumo-cocci elim. Staph. appeared	Moder-ate imp.
11	Sc.	Sinusitis	Gm-dip. Gm +dip. (Hemo) Staph	+ − −	+ + +	+ + +	+ − +	Bac.	γ strep. Gm-dip. Diphther-oids	Elim. of gm +dip. & staph. Appearance of γ strep. & diphther-oids	Marked imp.
12	Wi.	Asthma Sinusitis Bronchi-ectasis Nasal polyps	Gm +dip. Staph Colif. bac. strep.	Not performed				Bac.	Staph Gm +dip. Colif. bac.	Reduction in no. of Colif. bacilli	Marked imp. short dura-tion
13	Un.	Asthma Sinusitis Bronchi-ectasis Nasal polyp	Gm-dip. Staph Colif. bac.	Not performed				Bac.	Staph Colif. bac.	Reduction in no. of Colif. bacilli	Moder-ate imp.
14	Si.	Sinusitis Asthma	B. strep. Staph Diphth. Gm-dip.	+ + + +	+ + + +	+ + + +	+ + + +	Pen.	Strep. Staph Gm-dip. Occ. pneum.	Elimin. of hemol. strep. & diphther-oids. Appearance of strep. & pneumococci	Marked imp.

TABLE VI. (*Continued*)

15	Ol.	Chronic sinusitis Allergic rhinitis?	γ strep. Staph Colif. bac.	+ + +	+ − +	+ + +	+ − +	Bac.	B. strep. Staph Proteus Colif. bacilli	Bacterio-logically worse. Appear. of hemol. strep. & P. vulgaris	Marked imp.
16	Wit.	Chronic sinusitis Allergic rhinitis	γ strep. Gm-dip. Gm-bacilli (Hemophilus) Diphther-oids	+ + + +	+ + + −	+ + + +	+ − − +	Pen. & Bac.	B. strep. Gm-dip. Diphther. Gm-bacilli (Hemophilus) P. vulgaris	Bacterio-logically worse. Appear. of hemol. strep. & P.vulgaris	Marked imp.
17	Zin.	Sinusitis Asthma	γ strep. Gm-dip.	+ +	+ +	+ +	+ +	P&B & S.	Gm-dip. Colif. bacilli	Disappear-ance of γ strep. Appearance of Colif. bacilli	Un-im-proved

†Code to Sensitivity Studies: +inhibitory action; −no inhibitory action; ± partial or temporary inhibition.

*Hemolysis on patient's blood and not on rabbit's blood.

**Hemolytic staph. found in two sisters and subsequently isolated from the mother.

adequate culture studies were obtained before and after treatment. One of these patients was treated with large doses of penicillin only (after preliminary treatment with penicillin and bacitracin), seven with bacitracin only, six with a combination of penicillin and bacitracin, and three with these antibiotics plus streptomycin. Based on this small series of patients, it was noted that there was some limited correlation between the bacteriologic and clinical improvement. Thus, of fifteen patients who showed definite improvement, nine showed corresponding change in the organism found and suspected of pathogenicity. In two other instances, there was no change in the original organisms, but there was a definite reduction in number as judged by the number of colonies per culture plate. There may, therefore, be a quantitative change which may be of importance. Likewise, it was noted that among those clinically improved[15] there were two instances where, on a bacteriologic basis, they were considered possibly worse. One patient who was clinically unimproved showed no bacteriologic change.

The series of patients in whom pre-treatment and post-treatment cultures were obtained is too small at the present writing to draw any definite conclusions concerning the correlation between clinical results and bacteriologic changes.

ABSORPTION OF BACITRACIN VIA THE LUNGS

Studies of blood absorption of penicillin[11] and streptomycin aerosols[13] have previously been made by the senior author in collaboration with others, which have indicated that these antibiotics are readily absorbed from the respiratory tract. It was, therefore, of interest to investigate the absorption of bacitracin aerosol.

Seven normal males with good vital capacities were, therefore, treated with bacitracin (67,000 units), utilizing the breathing box method, and a

single blood sample was taken thirty minutes from the onset of treatment, which lasted about fifteen minutes. In the aforementioned studies with penicillin and streptomycin, maximum blood levels were obtained by that time. In none of these cases was any bacitracin demonstrable in the blood.† One asthmatic patient (Case 6, Table VI) who had been getting large doses of bacitracin was also examined for the presence of bacitracin in his blood one hour after treatment with 67,000 units, and likewise failed to show any absorption. This would indicate that the clinical evaluation of bacitracin as an aerosol would be an expression of its topical action, in sharp contrast to penicillin and streptomycin aerosols, which have twofold action, topical and systemic, following absorption.

There is the possibility that bacitracin may be absorbed to some degree in patients suffering from bronchiectasis.* This may possibly be accounted for by increased absorption across inflamed or altered mucous membranes. Care should therefore be exerted in the treatment of these patients by frequent urinary examinations in order to avoid possible nephrotoxic action.

ADVERSE REACTIONS

Although there was no definite proof of unfavorable reactions to bacitracin, it was suspected in two cases. One patient treated with bacitracin aerosol, who was also given bacitracin lozenges because of a pharyngitis, complained of a burning sensation in the throat following its use. She subsequently developed a similar sensation retrosternally when bacitracin aerosol was administered. This patient originally had complaints suggestive of a tracheitis along with asthma and sinusitis, and it is therefore difficult to evaluate the reaction to bacitracin aerosol. There was a definite unfavorable reaction to the lozenge, and, therefore, bacitracin in any form was discontinued.

Another patient on combined bacitracin-penicillin aerosol reported nasal irritation after the third treatment, which might have been caused by either antibiotic. Although the sinusitis was clinically improved, treatment was discontinued after the fifth day because the patient had to leave town, which prevented the discovery of the cause of the discomfort.

As for penicillin reactions, it is noteworthy that of the eighty-three patients only one developed a black tongue while under treatment with large doses of penicillin every six hours around the clock, including penicillin powder twice daily at home (Case 5, Table VI). Another patient developed a circumoral contact dermatitis on combined bacitracin-penicillin which disappeared completely with the removal of penicillin. Treatment was continued with bacitracin, and a cure was ultimately effected (Case 10, Table III).

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*Personal communication from Dr. Frank L. Meleney.

DISCUSSION

From our small series of patients treated exclusively with bacitracin, no definite conclusions can be drawn. It does suggest, however, the possibility that bacitracin aerosol may be equally as effective as penicillin aerosol. This conclusion must of necessity be qualified, due to the fact that the optimum dosage of bacitracin has, as yet, not been determined, and therefore it is possible that some of our patients may have been undertreated, making a true comparison impossible at this time. One can be more definite, however, regarding the combined action of bacitracin and penicillin aerosol, as compared with penicillin aerosol alone, in view of the larger series of eighty-three patients observed. Here we have noted a definite improvement in results. On this combined therapy, the favorable (moderately and markedly improved) cases reached 85.6 per cent compared to 73 per cent in a comparable series on penicillin alone. (This series included some of the earlier cases treated with penicillin, some of whom were limited to 500,000 units, which would be considered inadequate today.) This strongly suggests a clinical synergistic action and tends to confirm the bacteriologic synergism previously reported.[4,15] It is also possible that an additional explanation of improved results is due to the particular value of bacitracin in mixed infections, where the enzyme penicillinase is more likely to be produced, inhibiting the action of penicillin but not of bacitracin.[7]

The authors are cognizant of the limitations of the bacteriologic methods employed in this investigation. *In vitro* studies eliminate the host factor which is of great importance. Also, emphasis was placed on a pharyngeal culture, whereas cultures of the nose, throat and sputum may have been more informative. Then, again, a single method of culture was employed, and it is conceivable that some organisms may have found the medium employed unfavorable for growth and thus escaped detection. The question also arises whether the organisms obtained by culture of material from the surface of a membrane are actually the noxious agents since, in chronic disease, the organisms may be deep-seated within the mucous membrane. And, finally, what is a normal flora and when is a specific organism pathogenic? Some organisms, such as N. catarrhalis or nonhemolytic streptococci, may be considered as nonpathogens for most people, but is that true for all? We have observed hemolytic staphylococci in two sisters (Table VI, Cases 7 and 8) who were clinically ill and who improved remarkably with antibiotic therapy, yet the post-treatment cultures still showed hemolytic staphylococci. Are these organisms no longer pathogenic or is this only a transient state? Many questions still remain to be answered.

It has been the impression of the authors that frequent infections of the respiratory tract, particularly in children, were due to contact with carriers in the immediate family.[11,12] This was dramatically shown in the

cases cited above, in which hemolytic staphylococci were cultured from two sisters—one acutely and the other chronically ill with respiratory infections. It was inferred that the infection had spread from the older sister (chronic infection and some immunity) to the younger sister who was acutely ill and apparently with little or no immunity. But where did the older sister get the infection? Pharyngeal cultures were made, therefore, of both the mother and father, and the former was indicted as a possible carrier by the presence of a hemolytic staphylococcus, presumably the same found in the children.

This observation is of importance since it confirms bacteriologically a clinical impression previously voiced, and adds emphasis to the importance of treating simultaneously other members of the family, when necessary, in order to reduce the illness of a susceptible (nonimmune) patient. The bathroom method for aerosol therapy, previously described, is the answer for the younger child and a suspected parental or sibling carrier.

From a prophylactic angle, in reference to the cases cited above, it may be important to treat the mother at the first sign of a "cold," in order to prevent possible reinfection in the children. Likewise, the children, now well, will be given prophylactic aerosol therapy at the first sign of a "cold" in order to obviate a return of the original complaint.[11,12]

Bacitracin is of particular value not only because of its local topical action which enhances its value as an aerosol but also because it may be used in patients sensitive to penicillin. Thus, Case 12 in Table III exemplifies successful therapy with bacitracin in an individual who was previously found hypersensitive to penicillin. Likewise, Case 10 in the same table revealed a hypersensitivity to penicillin while under treatment with combined bacitracin-penicillin aerosol. Penicillin was discontinued, and the bacitracin alone achieved the desired therapeutic results.

In previous reports, one of us (S.J.P.) emphasized the importance of improving the vital capacity of patients with infective asthma, prior to aerosol treatment with antibiotics.[11] We wish to re-emphasize this point and advise the use of aminophylline and/or Isuprel, either in single or combined aerosols, to insure better utilization of the subsequent antibiotic.

The poor absorption of bacitracin from the respiratory system should minimize the fear of nephrotoxicity or any other systemic reactions. In our series of cases, urinalysis revealed an occasional slight, transient albuminuria. One patient treated under our supervision, but not included in this study because of inadequate therapy, manifested some evidence of the nephrotoxic action of bacitracin. She was given aerosol therapy with bacitracin (40,000 units twice daily) for only two days, and, in addition, bacitracin was administered intramuscularly, 10,000 units twice daily. She promptly developed albuminuria and many casts in the urine. Treatment was discontinued, and within a week the urine cleared.

One is led to speculate as to just what happens to substances such as

bacitracin, which are not readily absorbed from the lower respiratory tract. Studies with uranium oxide, administered to animals as an aerosol, show that when the aerosol particles are 0.5 micron or less in size, the aerosol is diffusely distributed throughout the bronchial tract and alveoli. Within twenty-four hours the bronchial system is cleared of the insoluble uranium oxide by ciliary action, and is eliminated through the gastrointestinal tract.[5] The aerosol may remain deposited in the alveoli, however, for months. This may not be true of bacitracin, inasmuch as bacitracin is a short-chain polypeptide,[1] which would probably be digested in time by enzymatic action.

CONCLUSIONS

1. Preliminary observations with bacitracin indicate that it may be safely and effectively employed in aerosol form for the treatment of sino-respiratory disease.

2. Although a true evaluation of bacitracin aerosol cannot be made at this time, in combination with penicillin it has been very effective and suggests synergistic action of these antibiotics.

3. Bacitracin is especially indicated: (a) when the cultured organism is sensitive to bacitracin but not to penicillin, as was shown in nine of ninety instances in our series; (b) in penicillin hypersensitivity or intolerence; (c) in mixed infections in which the neutralizing action of penicillinase may be a factor.

4. No absorption of bacitracin from the respiratory system could be demonstrated in these studies.

5. The definite value of bacterial studies, including bacterial sensitivity, is indicated.

6. No absolute correlation could be found between changes in bacterial flora and clinical results.

7. In repeated reinfections, especially in children, it may be important to search for and to treat any suspected carriers.

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DIATRIN HYDROCHLORIDE

A New Antihistaminic Agent for the Treatment of Pruritus and Allergic Dermatoses

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DIATRIN hydrochloride (N,N-dimethyl-N'-phenyl-n'-(2-thi-enylmethyl)-ethylenediamine monohydrochloride), a histamic antagonist of proven value in experimental animals,[2] had such a low incidence of side effects in recent clinical investigations[1] that a therapeutic trial was undertaken. A variety of pruritic and allergic dermatoses were chosen. The Diatrin was administered in 50 mg. tablets, both plain and sugar coated.*

RESULTS OF TESTS

Urticaria.—There were fourteen patients with urticaria, in five of whom it had followed the administration of penicillin. Of the latter, four were relieved in varying degrees—one completely, one moderately, and two slightly. One was not helped at all. The dose for all five patients was the same, 150 mg. daily. In the nine with urticaria from other causes, two of whom had angioneurotic edema as well, the dose administered to four was 200 mg., and to five, 400 mg. daily. Relief in all of these patients was prompt and complete.

Neurodermatitis.—Of three patients with disseminate neurodermatitis, one obtained marked relief on 400 and 1,000 mg. daily, one had moderate relief on 200 mg. per day, and one patient found 50 mg. at bedtime sufficient for his needs.

Dermatitis Medicamentosa.—Of three patients with generalized dermatitis medicamentosa, one did not respond, one exhibited moderate relief of pruritus, and one had varying degrees of relief on different occasions. This last patient had purpura following penicillin therapy.

Atopic Eczema.—Ten patients with atopic eczema were treated with 200 to 800 mg. of Diatrin a day for from eight to forty-seven days. Four were helped in varying degrees, and six failed to show any response. Of the former, two had only slight relief, one moderate relief from pruritus, and one had sporadic relief, sometimes complete and sometimes slight. The degree of relief was not dependent upon the dosage: for example, one patient was receiving 800 mg. daily with no effect, while one who received 250 mg. had very satisfactory results.

Erythema Multiforme.—Of three patients with erythema multiforme two showed no response to 200 mg. each day, but one had marked relief on the same dosage, with disappearance of the eruption in four days.

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*Diatrin hydrochloride was supplied by William R. Warner and Co., Inc. of New York, N. Y.

TABLE I

Diagnosis	Number of Patients	Relief			No Relief	Results	Side Effects
		Complete	Moderate	Slight			
Urticaria	9	9	—	—	—	100%	None
Penicillin Urticaria	5	1	1	2	1	80%	None
Neurodermatitis	3	2*	1	—	—	100%	None
Dermatitis Medicamentosa	3	1*	1	—	1	66%	None
Atopic Eczema	10	1*	1	2	6	40%	None
Erythema Multiforme	3	1	—	—	2	33.3%	None
Dermatitis Venenata	30	3	4	2	21	30%	2 patients with nausea, 2 with fever, 1 with vomiting, 1 with diarrhea, 1 with generalized burning of skin.
Infectious Eczematoid Dermatitis	4	—	—	1	3	25%	1 patient had nausea and urinary frequency.
Recurrent Vesicular Eruptions	9	1	—	—	8	11%	1 patient had nausea and vomiting.
Miscellaneous	4	2	1	—	1		
Total	80	21	9	7	43		

*The percentage values are somewhat misleading—first, because they are based on a small number of patients, and second, because the degree of relief varied and was in some cases inconstant.

Dermatitis Venenata.—Thirty patients with contact dermatitis were included in this series. Nine of these were helped; twenty-one were not. The dosage varied from 100 to 600 mg. daily. Here again there seemed to be no direct relationship between the daily dosage and results. For example, although one patient on 100 mg. per day was much more comfortable, there was no effect at all on other patients receiving the same dosage. One patient who was getting 600 mg. per day was completely relieved of pruritus; another on the same dosage felt no diminution in the intensity of pruritus.

Infectious Eczematoid Dermatitis.—There were four patients with intensely pruritic infectious eczematoid dermatitis. In three the itching was not allayed at all by 400 to 1,000 mg. daily, although one on 400 mg. felt somewhat better.

Recurrent Vesicular Eruptions.—This series included nine patients with recurrent vesicular eruptions of the hands and feet, not of the contact type. In eight of these there was no effect whatever from 100 to 400 mg. daily. The remaining patient had marked relief on 100 mg. per day.

Miscellaneous.—Diatrin hydrochloride was also given in doses of 100 mg. per day to two patients with herpes simplex, both of whom benefited. One patient with extensive insect bites received 200 mg. daily with no benefit. One patient with a pruritic pityriasis rosea took 100 mg. at bedtime and found the intensity of the pruritus relieved sufficiently to permit sleep.

SIDE EFFECTS

Minor side effects developed in seven patients; these included nausea, vomiting, diarrhea, urinary frequency, and generalized burning of the skin. In only three patients was it necessary to discontinue the drug. All side effects stopped promptly on cessation of the drug. As in previous experience with Diatrin,[1] the plain tablet was responsibile for all untoward reactions, the sugar-coated tablet in this admittedly small series being responsible for none. Aside from masking the bitter taste of the drug and thereby decreasing the incidence of nausea and vomiting, it is difficult to understand why a thin sugar coating should prevent the occurrence of these side effects. Possibly in a larger series, they would be more evident. However, even including those untoward effects for which the plain tablet was responsible, the percentage of side actions was remarkably low.

SUMMARY AND CONCLUSIONS

Diatrin hydrochloride was administered to eighty patients with allergic and pruritic dermatoses. Best results were obtained in urticaria, although other dermatoses responded to a lesser degree. These results are similar to those obtained with other antihistaminic agents. The incidence of side effects, however, was much lower than with other histamine antagonists at present in general use.

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POSSIBLE USES OF A DELAYED-ACTION ANTIHISTAMINIC

Clinical Trials

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THE desirability of properly timing and prolonging the purely sympomatic benefit which the newer antihistaminics afforded in reversible allergic disorders (notably urticaria and angioneurotic edema) soon became apparent. Accordingly, several drug manufacturers fulfilled a request to produce a four- to six-hour enteric-coated antihistaminic for clinical trial. Twenty-five mg. tablets of Thenylpyramine (N, N-dimethyl N'(2-thenyl)-N'-(2-pyridyl)-ethylenediamine) in this form were promptly furnished.* The average dose used was two tablets for adults and one for children.

The general subject of antihistaminic drugs has been thoroughly discussed previously,[1] and no new indications for the group can be added. The limitations imposed by the four- or five-hour effectiveness of the uncoated antihistaminics, however, suggested the following uses for the delayed action type:

1. The prevention of spontaneous allergic phenoména which regularly occur four to nine hours after retiring.
2. The prevention of delayed reactions from drugs, biologicals, immunizing allergens, et cetera, known to produce them between the effective time limits.
3. Prevention of nocturnal distress from willful ingestion of known food allergens.
4. Securing eight to ten hours of continuous action by the simultaneous ingestion of coated and uncoated antihistaminic drugs. This system can (a) eliminate mid-day doses for absent-minded, busy or sensitive people, (b) allow continuous relief throughout the night by bedtime dosage only, and (c) assure an allergist at least nine or ten hours of prophylaxis from constitutional reactions, without alarming the apprehensive patient.
5. Prevention of gastrointestinal disturbances produced by the uncoated drug.

Since the enteric-coated Thenylpyramine is pharmacologically no different from the uncoated, other than in its site and timing of absorption, it was tried only in cases in which the uncoated drug was known to be effective. The object was to test a method of administration only, for data on the type and percentage of cases benefiting was already known.[2,3] All subjects served, therefore, as their own controls. When nocturnal effectiveness was under investigation, the subjects had previously been roused by alarm clock to take the uncoated drug.

The results are shown in Table I.

*Supplies furnished through courtesy of Eli Lilly and Co.

TABLE I. RESULTS WITH PLAIN AND ENTERIC-COATED THENYLPYRAMINE

(A) Type of case	(B) Total cases	(C) Cases benefiting from uncoated drug	(D) Cases from Col. C in which enteric-coated drug tried	(E) Cases in which enteric-coated drug produced desired effect
Constant urticaria**	25	21 (84%)	21	21
Late night and early a.m. urticaria**	10	9 (90%)	9	7
Hay fever, seasonal	49	30 (61%)	28	26
Perennial allergic rhinitis	26	8 (30%)	8	6
Delayed reactions from injected allergens	25	23 (92%)	20	17
Gastrointestinal allergy (intentional ingestion)	16	5 (31%)	5	5
Nocturnal urticaria from afternoon injection of penicillin (Proc. or POB)	4	4 (100%)	4	3
Urticaria and local reaction from Globin Insulin	2	2 (100%)	2	2
Urticaria and local reaction from Protamine Zinc Insulin	2	2 (100%)	2	2
Asthma, seasonal	16	5 (31%)	5	4
Asthma, perennial	31	3 (9.7%)	3	2
	206	112 (54%)	107	95 (89%)
Gastrointestinal irritation from uncoated drug	19		19	16 (84%) prevented

**Many of the urticaria cases also had angioneurotic edema.

SUMMARY AND CONCLUSIONS

The uncoated Thenylpyramine afforded moderate to complete clinical relief or prevention of symptoms for 112 (54 per cent) of 206 allergic individuals. The enteric-coated drug, with a four- to six-hour delay in action, seemed theoretically indicated under certain circumstances listed above. It was accordingly tried on 107 of the aforementioned relieved group of 112, with prevention of symptoms in ninety-five (89 per cent); thus, the practicality of this mode of administration for procuring delayed action was verified.

Nausea and epigastric distress from uncoated Thenylpyramine are relatively slight compared to the other antihistaminic drugs in common use, occurring in nineteen of the 206 cases (9 per cent). (In only one-fourth of these was discontinuance necessary.) These symptoms in this group of nineteen patients were abolished in seventeen by the use of enteric-coated tablets, but the other usual side reactions to antihistaminic drugs were not diminished; they were merely made more difficult to identify. It is obvious that the uncoated tablets should always be tried first in order to allow such idiosyncrasies to be identified more easily.

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SENSITIVITY TO KELCOLOID
Preliminary Study

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THE COMMON water-soluble gums of importance, other than algin, are locust bean gum (Carob bean gum), karaya, acacia (gum arabic), tragacanth and Irish moss extract (carrageenin). Human hypersensitivity to these substances has previously been recognized and reported.[1,2]

Algin is the common name for designating alginic acid and its derivatives. Algin compounds are sodium alginate, potassium alginate and ammonium alginate.

Alginic acid is the hydrophilic colloidal polymer of anhydro-B-D-mannuronic acid that is extracted from various species of brown algae. It is primarily derived from giant kelp, Macrocystis pyrifera. Propylene glycol esters of fatty acids have previously been shown to have no significant toxic effects.[3] Propylene glycol itself is well tolerated in medicinal preparations used orally, parenterally, and as aerosols. Kelcoloid* is the propylene glycol ester of alginic acid (propylene glycol alginate).

Because of their hydrophilic colloidal properties, these algin products are used as thickening, suspending, stabilizing, emulsifying, gel-producing, film-forming, and adhesive agents in numerous food and industrial products. The alginates in general are utilized in ice creams, sherbets and ices, chocolate milk, cheeses, puddings, bakery goods, confectionaries, jellies and syrups, breads, pharmaceuticals, cosmetics, shampoos, shaving creams, toothpastes, paper coatings and sizings, adhesives, textile printing and sizing, water emulsion paints, boiler compounds, welding rod coatings, leather finishings, ceramics, insecticides, cleaning compounds, detergents, polishes, et cetera. Ammonuim alginate is used primarily in creaming and thickening natural and synthetic rubber lattices and rubber compositions, in water paints and wherever the presence of sodium is objectionable. Potassium alginate is most commonly used in dental impression compositions.

Kelcoloid, like other algin products, gives viscous aqueous solutions at relatively low concentrations. It is used as an emulsifying, thickening, stabilizing and suspending agent, in many food and industrial preparations. Unlike sodium alginate, it is soluble in acid solutions. It has pronounced emulsifying properties which make it excellent for use in acidic media such as flavor emulsions, French dressings and salad dressings. It is also used as a stabilizer and thickener for meat sauces, meringues, syrups and toppings. It is found in certain pharmaceutical and industrial products such as medicinal jellies, mineral oil emulsions, industrial polishes and cleaning compounds.

Presented at the Fifth Annual Meeting of The American College of Allergists, April 14-17, 1949, Chicago, Illinois.

*Manufactured by the Kelco Company of San Diego.

METHOD OF STUDY

An attempt has been made to study possible human hypersensitivity to Kelcoloid, and investigations were carried out in the following manner: Fifty individuals known to be allergic to numerous inhalants and foods were tested intradermally to various dilutions of Kelcoloid. As a control, fifty individuals without an allergic history and without a familial history of allergy were also tested.

Individuals giving skin reactions considered to be significantly positive were tested by the indirect (passive transfer) method. In those instances where direct and indirect positive skin tests were obtained, the patients were fed varying amounts of the preparation in order to note the clinical effect.

The results of the skin reactions of both groups of individuals are shown in Table I.

TABLE I

Allergic Individuals				
+ —	+	+ +	+ + +	+ + + +
(Irritative)	Very Slight	Slight	Moderate	Severe
5 cases	6 cases	3 cases (1—delayed)	2 cases	None
No reaction—33 cases				

Nonallergic Individuals				
+ —	+	+ +	+ + +	+ + + +
(Irritative)	Very Slight	Slight	Moderate	Severe
7 cases	3 cases	None	None	None
No reaction—40 cases				

It will be noted that no severe skin reaction occurred in either the allergic or the nonallergic group. Moderate reactions occurred in two cases in the allergic group, and none in the nonallergic group. Slight reactions occurred in three cases in the allergic group, one being a delayed reaction, and none in the nonallergic group. Very slight reactions occurred in six allergic individuals and in three cases in the nonallergic group. Irritative reactions occurred in a total of twelve cases.

Of the allergic group, five persons giving significantly positive skin reactions (slight to moderate) were tested by the indirect method. These gave positive passive transfer tests. Three of these individuals, when fed amounts of Kelcoloid somewhat greater than would normally be ingested as food, reproduced their usual allergic manifestations to a mild degree. This occurred each time the preparation was administered.

CONCLUSIONS

The results of sensitivity studies on Kelcoloid indicate that only a very small percentage of the allergic population shows evidence of clinical sensitivity. No significant sensitivity could be demonstrated in a group of

(Continued from Page 718)

OBSERVATIONS ON THE ACTION OF ORTHOXINE IN PATIENTS WITH BRONCHIAL ASTHMA

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SINCE the majority of sympathomimetic drugs now in use for the symptomatic relief of asthma are associated with a relatively high incidence of undesirable side reactions, current efforts in the development of new antiasthmatic drugs are being directed toward the synthesis of bronchodilator substances which lack strong vasopressor action and central nervous system-stimulating effects. One recent development along these lines is the n-isopropyl amine derivative of epinephrine (Isuprel), which not only divorces bronchodilator action from pressor effect but is associated with a strong vasodepressor response.[5] This compound, however, also presents certain limitations in its clinical use. Its oral action is questionable, and when injected it is frequently accompanied by profound stimulation of the heart and a precipitous fall in blood pressure. The most satisfactory clinical application of this drug has been by inhalation.[7] A more recent development which shows considerable promise, is the synthesis of the orally active drug, Orthoxine* (ortho-methoxy-B-phenyl-isopropyl methylamine hydrochloride). In the experimental animal this drug is more effective than ephedrine in relieving bronchoconstriction; it induces practically no pressor response, effects less central nervous stimulation, and has no greater toxicity than ephedrine when administered orally.[6] Curry, Fuchs, and Leard[1] have found the drug effective by mouth in bronchial asthma and in asthma-like attacks induced by the parenteral injection of histamine and methacoline. Wittich[8] observed a beneficial effect not only in asthma but in some cases of seasonal hay fever and allergic headache.

The following observations were made in a group of ambulatory patients with chronic asthma, all of whom had been followed for some period of time in the out-patient clinic or in private practice. Orthoxine was administered orally in these patients, and its effect was noted on symptoms of asthma, vital capacity, pulse and blood pressure. Since all of these individuals were taking or had taken ephedrine for symptomatic relief in the past, an effort was made to elicit any history of intolerance to this drug. An accurate comparison with the effects of Orthoxine could therefore be made, especially in those who had experienced rather profound side reactions from small doses of ephedrine.

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*Orthoxine was supplied for this study by the Research Division, The Upjohn Company, Kalamazoo, Michigan.

TABLE I. EFFECT OF ORTHOXINE ON VITAL CAPACITY OF ASTHMATIC PATIENTS

Patient	Dose mg.	Degree of Asthma (mild—mod.—severe)	Vital Capacity in c.c.					Symptomatic Effect (excellent—good—fair—negative)
			Before	After				
				15min.	30min.	45min.	60min.	
J.G.	100	Moderate	2200	2400	2600	2600	2600	Good
F.R.	100	Moderate	2600	2400	2600	2600	2600	Good
W.P.	100	Moderate	2000	1800	1800	1600	1800	Negative
R.E.	100	Mild	2400	2600	2800	3000	3000	Excellent
S.G.	100	Moderate	2200	2600	2400	2200	2200	Fair
J.S.	200	Moderate	1600	1800	2200	2200	2200	Negative
M.M.	200	Moderate	2200	2800	2800	2800	2800	Excellent
N.W.	200	Severe	1800	1000	1200	1800	1800	Negative (required i.v. aminoph.)
E.O.	200	Severe	1800	1800	2200	2600	2600	Excellent
P.W.	200	Moderate	2000	1800	1800	2000	2000	Negative
F.K.	200	Severe	1000	800	1200	1200	1400	Fair
R.E.	200	Mild	2400	2000	2000	2800	2800	Good
C.N.	200	Severe	1000	1000	800	——	——	Negative (required i.v. aminoph.)
G.M.	200	Moderate	2400	2400	2400	3000	3000	Excellent

VITAL CAPACITY

The effect of Orthoxine on vital capacity was observed in fourteen ambulatory patients who presented themselves in the office or out-patient clinic with symptoms of asthma. Determinations were made with the McKesson-Scott apparatus prior to the ingestion of 100 to 200 mg. of Orthoxine, and at fifteen-minute intervals during the next hour. Auscultation of the chest was carried out before and after the drug was taken, and the degree of asthma classified as mild, moderate, or severe (Table I).

An increase in vital capacity was recorded in nine cases during the period of observation. All but one of these patients experienced a favorable symptomatic effect. Vital capacity readings were unchanged or slightly decreased in five other subjects during the one-hour period following ingestion of Orthoxine. One of these patients obtained symptomatic improvement despite failure to show an increase in vital capacity, while the remaining four required other measures to relieve their asthma. Two responded to inhalations of Isuprel, and two required intravenous aminophylline. The findings on chest examination before and after Orthoxine in most instances paralleled the recorded changes in vital capacity.

CARDIOVASCULAR EFFECT

The effect of Orthoxine on the cardiac rate and blood pressure was noted in eighteen asthmatic patients. Observations were made before the drug was administered and at regular intervals for one hour following its ingestion (Tables II and III).

An increase in pulse rate of 10 beats per minute or more was recorded in six subjects; a decrease of the same degree occurred in three subjects; variations in the remaining nine cases were less than 10 per min-

TABLE II. EFFECT OF ORTHOXINE ON PULSE RATE

Patient	Dose mg.	Resting Pulse	Pulse After Orthoxine			
			15 min.	30 min.	45 min.	60 min.
I.M.	100	72	92	88	88	84
L.G.	100	60	60	60	60	60
S.W.	100	72	72	72	80	72
H.T.	100	90	82	88	88	88
M.G.	100	84	88	84	76	76
S.L.	100	112	104	100	96	96
L.S.	100	88	88	88	88	88
G.S.	100	72	78	72	72	72
I.G.	100	78	78	78	78	78
F.R.	100	72	78	72	72	84
J.S.	200	102	96	120	120	120
M.M.	200	114	102	108	102	102
N.W.	200	84	72	90	84	84
L.O.	200	78	88	86	84	84
W.P.	200	108	108	120	112	112
R.E.	200	112	108	100	108	108
F.W.	200	108	116	120	120	120
C.N.	200	120	116	120	120	120

TABLE III. EFFECT OF ORTHOXINE ON BLOOD PRESSURE

Patient	Dose mg.	Resting Blood Pressure	Blood Pressure After Orthoxine			
			15 min.	30 min.	45 min.	60 min.
I.M.	100	130/70	118/68	120/70	120/70	120/70
L.G.	100	142/80	124/70	118/60	124/65	130/70
S.W.	100	120/80	110/80	104/76	115/80	115/80
H.T.	100	102/60	100/60	98/64	96/60	100/60
M.G.	100	142/90	130/90	130/90	130/90	130/90
S.L.	100	110/80	110/80	108/80	110/80	110/80
L.S.	100	150/110	154/106	160/104	154/110	154/110
G.S.	100	190/98	160/94	144/90	160/96	160/94
I.G.	100	110/66	110/64	110/64	110/66	110/64
F.R.	100	168/98	154/94	128/90	120/89	132/80
J.S.	200	172/120	180/120	172/120	164/120	170/120
M.M.	200	148/110	158/104	140/100	144/104	144/110
N.W.	200	112/80	104/80	108/80	104/80	104/80
E.O.	200	104/80	96/80	100/80	98/80	96/80
W.P.	200	122/100	122/90	120/86	100/80	100/80
R.E.	200	110/60	96/60	100/60	100/60	100/60
F.W.	200	100/70	88/62	82/58	94/62	96/62
C.N.	200	100/70	100/70	100/70		

ute. In no instance did the change in pulse rate exceed 20 beats per minute.

A fall in systolic blood pressure of 10 to 44 points was recorded in nine subjects, associated in five cases with a decrease in the diastolic level of from 10 to 20 points. The greatest drop occurred in those with abnormally elevated readings prior to ingestion of the drug. An increase of 10 points in the systolic pressure was recorded in only two subjects. No significant increase in diastolic pressure occurred. In two cases there was a slight increase in pulse pressure.

ANTIHISTAMINIC ACTIVITY

This phase of action was briefly investigated on the basis of Wittich's report that some patients with hay fever and allergic headache were benefited by Orthoxine.[8] Guinea pigs which were given 100 to 200 mg./kg. of the drug intraperitoneally failed to survive one lethal dose of histamine administered intravenously fifteen minutes later. Inhibition of histamine

whealing in normal human skin, as determined by techniques developed for the assay of antihistaminic drugs,[3] was negligible. It would appear, therefore, that antihistaminic activity of Orthoxine, if present, is not of the same order shown by the so-called "antihistaminic drugs."

CLINICAL EFFECT

Sixty-one patients with asthma were given 100 mg. tablets of Orthoxine. They were advised to take one as necessary for the relief of difficulty, and to repeat the dosage at four-hour intervals if symptoms recurred. Thirty-seven of these reported symptomatic improvement beginning within five to thirty minutes after ingestion of the drug, and lasting for at least one hour, and in some cases for as long as twelve hours. Twenty-four patients obtained no relief following the use of the drug in doses of 100 mg. Six of these experienced a good symptomatic effect when the dose was increased to 200 mg. In twenty-four additional patients, a dose of 200 mg. produced a good response in nineteen, while five others reported no improvement. In those who continued to use Orthoxine over a period of time for symptomatic relief, it was noted that mild or moderate attacks usually responded quite well to the drug, while unusually severe asthma frequently required measures beyond orally ingested medication for relief.

SIDE EFFECTS

Fifteen patients in the group of asthmatics who were given Orthoxine were known to be extremely intolerant to small doses of ephedrine. Ephedrine and ephedrine-like drugs usually produced in these patients symptoms such as nervousness, insomnia, tremor, vertigo, headache, and palpitation. Twelve of the fifteen were able to take 100 to 200 mg. doses of Orthoxine without experiencing such effects. Three others reported relatively mild symptoms of central nervous system stimulation. One of these experienced such effects only from 200 mg. doses and was able to tolerate 100 mg. amounts very well. In the entire group of eighty-six patients who received Orthoxine, nausea was reported in eight cases following large doses of the drug taken on an empty stomach. In some instances this was not present when the dose was reduced to 100 mg. or when it was taken immediately after meals. One patient reported a "choking sensation" with increase of asthma following ingestion of the drug.

DISCUSSION

In developing new sympathomimetic drugs which divorce bronchodilator action from pressor effect, it should be recalled that both of these characteristics are probably important as far as the relief of the asthmatic paroxysm is concerned. The action of epinephrine on the bronchial tree is twofold: first, relaxation of the bronchial musculature, and second,

vasoconstriction with reduction in the swelling of the mucosa. The latter is very likely as important as bronchodilation in affording relief in asthma. Very frequently, however, vasoconstriction is followed by a prolonged inhibitory phase, with vasodilatation and congestion of the mucosa, and may very likely be related to the "epinehrine-fastness" so frequently encountered in severe asthma. Such "after-congestion" is also seen in the nasal mucous membrane following the use of epinephrine as well as other strong local vasoconstrictors.[2] With epinephrine, this effect may be related to the vasodilator component of its action, but in the case of other strong vasoconstrictors it appears that another mechanism, probably a compensatory reaction, is involved. The constrictor effect of ephedrine on arterioles is less marked than that of epinephrine, and a vasodilator component in its action is not demonstrated. An increase in pulse rate, blood pressure and cardiac output is usually associated with its clinical use. Patients with hyperthyroidism and hypertension may be more sensitive to its action than normal persons. Ephedrine influences respiration in two ways: by bronchodilation and by direct stimulation of the respiratory center. In addition, however, it is a strong central nervous system stimulant, which accounts for the majority of its side effects.[4]

Orthoxine affords relief in bronchial asthma principally through its bronchodilator effect, which from experimental studies is found to be considerably greater than that of ephedrine. Clinically, a 100 mg. dose of Orthoxine produces a response in asthma approximately equivalent to that of a 25 to 50 mg. dose of ephedrine. The effectiveness of the smaller amount of ephedrine is very likely the result of vasoconstriction and respiratory stimulation added to its bronchodilator action. The larger dose of Orthoxine, however, is often clinically effective without producing the undesirable side effects which so frequently accompany the use of ephedrine. Its minimal effect on cardiac rate, and the lack of pressor response, would indicate that Orthoxine is a desirable drug in the asthmatic patient with hypertension or other cardiovascular disease. The relative infrequency of central nervous system stimulation allows its use in many who are unable to employ other orally effective agents for the relief of asthmatic symptoms.

SUMMARY

1. Orthoxine (ortho-methoxy-B-phenyl-isopropyl-methylamine hydrochloride) is a new, orally effective, synthetic bronchodilator substance, whose action is not associated with strong vasopressor activity or central nervous system-stimulating effects.

2. The average orally effective adult dose of Orthoxine is from 100 to 200 mg. An increase in vital capacity frequently follows this amount of drug, while relatively little alteration in cardiac rate is seen. A slight drop in systolic blood pressure, more pronounced in those with hypertension, may occur.

3. Side effects from Orthoxine are mild and relatively infrequent. Many patients who are extremely intolerant to ephedrine are able to take a clinically effective dose of Orthoxine without difficulty. Nausea and mild central nervous system-stimulating effects are occasionally seen.

4. The clinical effectiveness of Orthoxine in bronchial asthma, its lack of pressor action or cardiac and central nervous system stimulation, suggests its use in place of ephedrine, especially where hypertension, cardiovascular disease and side effects preclude the use of ephedrine.

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Progress in Allergy

HAY FEVER
A Review of the Literature of 1948

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Although a considerably larger number of articles on this subject appeared in the world's literature in 1948 than those upon which we reported last year,[105] we regret that basic advances of note were lacking. Dan Campbell[37] stated that he "cannot help but feel that many of the underlying causes of hypersensitivity reactions in man are intimately associated with phenomena of immunity, and that an immunochemical approach to the problem of allergy is of fundamental importance." In turn, we cannot help but subscribe to these feelings.

BOTANY AND POLLEN SURVEYS

O. C. Durham's[59] report on airborne allergens in the National Parks reveals an intensive study of the pollens found during the period the parks are open to the public. Many are ragweed free or are relatively so. Among those free are Bryce Canyon, Glacier, Grand Canyon, Grand Teton, Isle Royale, King's Canyon, Mt. McKinley, Mt. Rainier, Olympic, Sequoia, Yellowstone, and Yosemite National Parks.

Targow,[175] reporting on a pollen survey of the Los Angeles area over a five-year period, notes that pollen counts are relatively low when compared to the Midwest; however, the seasons are more prolonged and overlapping. Trees pollinate intermittently from January to November; grasses pollinate in March, reach a peak late in May or early June, then gradually decline to about mid-December. Weeds begin with chenopods and amaranths in March, followed by ragweeds in April and artemesia in June. Peaks reached by ragweeds are minimal in May and maximal from August to October, followed by artemesia in September, October and November.

Deppe,[54] in a discussion of the hay-fever pollens in the Seattle area, notes that there are no ragweeds west of the Cascade Mountains. The Cascade Mountains are a natural barrier and divider for the variation in pollens found in the upper northwestern part of the United States. The two main tree pollens are the alder in April and the willow in May. Other offenders are: hazel, maple, ash, birch, elder, dogwood and poplar. The grasses which pollinate from mid-May to July are: june, orchard, stallion, and perennial rye, velvet, timothy and red top. The weeds pollinate from July to frost. The chief offenders are: plantain, sheep sorrel, pigweed, lamb's quarter and curly dock.

Shure and Harris,[164] of Los Angeles, point out that ragweed pollen cases will be in trouble in southern California from western ragweed, burr ragweed and slender ragweed pollen. Furthermore, the ordinary grass-and-weed case of the East will sooner or later in southern California have hay fever from February through November.

Wine,[187] in discussing the "X-Hay Fever Problem in the South," stated that it is limited to the middle of South Carolina, the southern two-thirds of Georgia, Alabama, northern Florida, the western tip of Tennessee, Mississippi, Louisiana

and southeastern part of Texas. The offending agent is present in the air from May to October. Complete relief is obtained when the affected individual leaves the area or goes to the seashore.

Wolf,[193] reporting on a fall-pollinating red berry juniper, finds this tree distributed over parts of central and west Texas, southwestern Oklahoma and southeastern Arizona. It has been identified as Juniperus pinchoti (Sudworth), or red berry juniper. It closely resembles J. ashei, but it pollinates from the latter part of September to early in December and is introducing another pollen season in the areas involved. The cedar promises to become more profuse and more widespread due to the fact that it regenerates from roots and cannot be killed above the ground. It is similar antigenically to J. ashei and is a significant cause of hay fever.

E. H. Walzer, Siegel, Chait and M. Walzer,[184] in their second series of surveys of ragweed pollination in Greater New York Metropolitan District, include localities within a 50-mile radius of New York City. The technique employed was approved by the Pollen Survey Committee of the American Academy of Allergy. The pollen density in this area was comparatively low in 1947. The highest seasonal total count for the city was obtained at the Staten Island station. The remaining city stations listed in the order of decreasing pollen density were as follows: Flushing, Manhattan, Rockaway, Jamaica, Bronx, and Brooklyn. Three peaks in the pollen season were noted at most of the stations included in the survey. The first occurred during the last week in August; the second, which was the greatest, during the first week of September, and the third during the second week of September. Because of the relatively light pollen season, the influence of the ragweed extermination program on the ragweed counts, in this city, could not be evaluated.

Claus,[41] in a study of the anemophilous plants of Puerto Rico, found that some wind-pollinated species are similar to those found in the United States. Marchand[124] reports on hay-fever plants of Puerto Rico, and says that pollinosis does occur in Puerto Rico from grasses and amaranths. Bermuda grass is found from November to February. The chief amaranth offender is spiny amaranth. Sugarcane pollen is found all year around. Trees are present, but pollen from the Australian pine is the only one suspected. Artemesia are rare.

Gottlieb,[79] discussing a note appearing in the *JAMA* on the book notice of "Diseases of Children," edited by Patterson of England, found nothing surprising in the statement that "nothing is said about hay fever caused by giant and dwarf ragweed, or about desensitization against this type." Ragweeds generally do not exist in the British Isles, and in fact are of no practical consequence in Europe. The only significant hay fever in Britain is that due to pollens of grasses.

Alford,[9] discussing allergy in Japan, indicates that it is in striking contrast to allergy in the United States. The climate and general topography of the country are such that grasses and ragweeds are not important factors in the causation of allergic symptoms. No records of seasonal hay fever were noted. Fifteen per cent of the land is under cultivation, and 50 per cent of the cultivated land is in rice. Fifty per cent of the land is forest with oak, ash, birch, elm and poplar predominating.

Greco and Bartos,[80] in a pollen survey in the air of the city of Santos, Brazil, found pollen present from June to September. The most common pollen is grass, of the variety of *Melinis minutiflora*. The total pollen count was very low.

Heise and Heise,[93] report on the distribution of ragweed pollen and Alternaria spores in the upper atmosphere. Counts of ragweed pollen and Alternaria spores in the upper atmosphere were made during flight. The greatest concentration of pollen occurred at 3500 feet. Cumulus clouds and surrounding atmosphere

contained many times the number of particles found in clear air away from the clouds. The level of maximum concentration of particles rose from early afternoon to 8:00 p.m., when it fell slowly until dawn.

Rooks[151] describes a device for the electrostatic precipitation of pollen and fungus spores upon a counting slide. This electrostatic precipitator is portable, and can sample volumetrically airborne pollen and fungus spores by the slide method and with additional essential instruments it is possible to determine the incidence of airborne bacteria and fungus spores by the culture plate method. This electrostatic precipitation, in which special glass slides with conducting surfaces are used with the prescribed instrument, offers a convenient, efficient and new approach to certain experimental problems involving airborne pollen and fungus spores.

Alemany-Vall[6] discussed rhinitis and asthma caused by pollen in Barcelona. The author made a definite attempt to find the etiological agent which is responsible, on the basis of the skin tests as well as surveys of the patients' surroundings. Many species of gramineous pollen were examined. These species were all found within the municipal boundaries of Barcelona from March to July. The pollen of Parietaria officinalis is a frequent cause of simple and complicated rhinitis after asthma. The scarcity of pollenosis asthma not preceded by pollenosis rhinitis due to the plant is discussed. Studies of hay fever showed that the nasal mucous membranes were red and irregularly swollen, even in old and stationary cases.

Blumstein[21] discussed the ragweed extermination plan of Philadelphia for the year 1948. The chemical 2,4-D (dichlorothenoxyacetic acid) was used. The plan was publicized in all newspapers and the health department notified of areas which were high in ragweed, and the trucks were then sent out to spray. The program was partially successful.

In 1946 the health department of Brooklyn had such a program and met with similar success. An interesting note on the Philadelphia study was the report of the pollen count of eight stations in different sections of the city. The pollen counts in these sections varied considerably. This is not an infrequent observation by many investigators who count pollen from different sections of a single city.

C. Juhlin-Danfeldt,[103] in an excellent article, reviewed the pollen situation of the northern countries of Europe. There are two hay-fever seasons in Sweden. The spring season is due to the trees, namely, Pinus, as well as Betual, Picea, Populus, Onecus, Juniperus, Anlus; the grass season occurs in the summer. There is a small amount of weeds belonging to the artemesia family. The patients are usually tested with birch pine, timothy, English plantain, sheep sorrel, lambsquarters, linden, oxeye daisy, and common mugwort. Of the people who are sensitive, 29 per cent are due to trees, 76 per cent due to grass, and 16 per cent due to the compositae. Treatment with the tree extracts in dilution of 1:10,000 to 1:1,000 are used, and grass extract in dilutions of 1:10,000 to 1:100,000 are used. The preseasonal and the coseasonal methods are the ones of choice.

FUNGI

A number of investigators have been studying the relationship of molds in outdoor air and indoor air. Newton, Scherago and Weaver[135] studied the mold distribution in outdoor air, indoor air and house dust, in eastern, central and western Kentucky. They found seasonal variations, with penicillium and phycomyces predominating. Some differences were noted in the various sections of the state, but were slight. Four genera previously not reported were encountered, namely, montospora, stemphylium, tetra-coccosporum, and phycomyces. Their observation that certain molds occur predominately in outdoor air, and others in house dust, points to their suggestion of including house dust, as well as air, in surveys of mold distribution.

Flensborg and Samsoe-Jensen,[71] using Feinberg's technique, cultured the outside air for mold spores by counting the number of colony growths on a five-minute exposure of a Petri plate. Marked variations in mold counts were noted. Hormodendrum was first noted in June, and it continued throughout the summer. Eighty to 120 colonies was the average count. Hormodendrum averaged 72 per cent of all colonies counted. Penicillium (9 per cent) was in the air during April and May. Alternaria (2 per cent) was at its height in August, and Pullularia (27 per cent) in July.

Flensborg and Samsoe-Jensen[72] reported on mold spore counts in Copenhagen during March to August, 1947. They found that Hormodendrum was highest, followed by Penicillium, Monilia, Pullularia, and Alternaria. Of the total number of spores counted, Hormodendrum was equal to 72.4 per cent, Penicillium 9.2 per cent, Monilia 2.4 per cent, Pullularia 2.2 per cent, and Alternaria 2 per cent. The predominant molds found indoors were of the genera Penicillium.

Ivar Nilsby,[71] discussing Flensborg's paper, reported on his results of mold spore counts of outdoor air compared to indoor air in Örebro. In outdoor air, Hormodendrum represented 68 per cent, Penicillium 11 per cent, Pullularia 6 per cent, yeast 3 per cent, Botyritis 1.5 per cent, and Aspergillus 1.3 per cent. In the indoor air Penicillium represented 43.5 per cent, Hormodendrum 27.5 per cent, yeastlike organisms 10 per cent, Aspergillus 6.2 per cent, Pullularia 5.6 per cent, Mucor 2.8 per cent, Alternaria 2.1 per cent, and miscellaneous 1.2 per cent.

M. Schwartz,[71] continuing the discussion of Flensborg's paper, reported that he cultured fungi from house dust. Among the varieties found, Penicillium was first, with 117 colonies; the others found were Aspergillus with 36 colonies, Mucor 29 colonies, Alternaria 19 colonies, Fusarium 15 colonies, Rhizopus 5 colonies, and Hormondendrum 3 colonies. From a simple house dust specimen, seven varieties of fungi were cultured, from which extracts prepared gave only two positive skin tests in the patient from whom the dust was obtained.

Reymann and Schwartz[147] reported on their studies of the occurrence of allergenic fungi found in house dusts for twenty-two Danish asthmatic patients. Their results were similar to the above studies in the variety and distribution of fungi. Six of the twenty-two gave positive cutaneous reactions to one or more of the fungi. Thirteen of twenty-two patients showed positive cutaneous reactions with autogenous house dust extracts, and five of thirteen had positive reactions to fungi cultured from their dust. In nine patients in whom autogenous house dust extracts were negative, one was positive to the fungi cultured from the dust. This would indicate that although there is no common antigen, one should test with extracts of fungi cultured from their house dust as well as the house dust itself.

Eisenstadt[62] reports that the dominant molds in the Minneapolis area are Alternaria, Hormodendrum, Helminthosporium, Aspergillus, Penicillium, Fusarium, Phoma, Mucor, Mycogene, and Pullularia; except for Penicillium and Aspergillus molds, they have a seasonal variation, becoming relatively few in the winter and profuse in the summer. Of 246 patients tested with eight different molds, and 124 tested with Alternaria and Hormodendrum, there were 34 per cent positive reactions (36 per cent tested with eight molds, and 33 per cent tested with Alternaria and Hormodendrum). Age incidence is similar to pollens, and multiple sensitivity is the rule. The tests were clinically significant in 29 per cent of the patients and of primary etiological importance in 11 per cent.

POLLEN PURITY

With the recommendations of Dr. Veldee,[180] of the United States Public Health Service, for the collection and preservation of pollens becoming accepted by the men

interested in collection and selling, as well as by the two national organizations interested in allergy, it is hoped that a start in the direction of standardized allergenic materials has been made. These specifications are listed under the headings, "Qualifications of the Pollen Collector," "Labelling the Dispensing Container," "Purity of the Pollen," "Stability of the Active Component of the Pollen," "Type of Container," "Changes of Color in the Dry Pollen," "Co-operation of the User," and "Collections of Pollen." No reports have appeared in this year's literature of gross contamination or mislabelling of pollens. It has been noted by many that different lots of the same type of pollen, collected in different localities, have different potencies when extracted by the same method. The potencies vary in their nitrogen content, protein nitrogen content, and in their biological skin activity.

IMMUNOCHEMISTRY

In past years, much knowledge in the field of allergy was stimulated by the active workers in the field of immunochemistry. It seems that since the rebirth of psychodynamics, basic investigations in allergy have been somewhat stifled. It is, therefore, with a great deal of regret, that the authors find little of noteworthy progress in this particular branch of allergy.

Wodehouse[192] reports interesting observations on patterns of allergic sensitization. Clinically, pollen-allergic patients of the multiple sensitization type generally have a single major sensitization upon which the others all depend. The pollen atopen has a mosaic structure similar to that found in the bacterial or animal cell, and is susceptible to analysis. It consists of a major antigen which is species-specific or group-specific, being shared, if at all, only by the phylogenetically closely related species. It has also a number of minor antigens which are common to the related and unrelated species in an unpredictable way. The minor antigens are capable of producing clinical symptoms.

Brown and Loveless[30] investigated the allergenic skin activity of low ragweed pollen after the extract was irradiated with ultraviolet light. One portion of a low ragweed extract was subjected to irradiation at 6 inches through a glass barrier for one hour, and another portion for thirty minutes. Both were compared with an untreated extract on ragweed-sensitive patients. The concentration of extracts which elicited threshold responses were compared. Cross neutralization studies were also made. It was noted that irradiation of low ragweed extract with the doses of ultraviolet light employed had no effect on the cutaneous reactivity of the extract.

Alexander, Johnson and Bukantz[7] studied the correlation between symptoms of ragweed hay fever and the titer of thermostable antibody. They find that there is a general lack of correlation of the above, as determined by the methods used and the degree of clinical protection afforded. The mechanism by which clinical improvement occurs following specific pollen therapy, remains unknown.

Hampton, Bukantz and Johnson,[87] in their studies on the deterioration of ragweed pollen extracts as measured by precipitation, neutralization and protein nitrogen analysis, with special reference to the prevention of deteriorization by glycerine, noted that glycerinated ragweed extracts showed no loss or less loss of activity than plain extracts after heating or storage at four different temperatures. Plain unglycerinated low ragweed extracts, upon heating to 56° C. for thirty minutes, and upon storage at room temperature, 6° C., minus 25° C., and minus 70° C. for periods up to one year, showed loss of activity as measured by their ability to precipitate anti-ragweed rabbit serum, and to neutralize skin-sensitizing antibodies of ragweed-sensitive human serum.

Bukantz, Johnson and Hampton[32] studied absolute colorimetric methods in the analysis of factors influencing precipitation of ragweed pollen extracts and homol-

ogous rabbit antisera. They used the quantitative microprecipitin technique of Heidelberger and MacPherson in the analysis of factors influencing precipitation of ragweed extracts and rabbit anti-ragweed serum. Refrigeration for forty-eight hours carried the precipitation to completion. There was least avidity of ragweed extract for rabbit anti-ragweed antibody in the region of considerable antibody excess. Striking differences were noted for two ragweed extracts in the relation between their protein nitrogen content and the total nitrogen precipitated from a single rabbit serum. The precipitinogenic activity of ragweed extracts diminished progressively during storage in the frozen state. A few preliminary experiments described the effect of "blocking" antibody upon this precipitating system. Normal serums were found to possess some inhibitory activity but much less than that observed with sera from treated ragweed subjects. The degree of inhibition by normal serum was unaffected by altering the conditions of precipitation in a manner which increased the effect of serum from treated ragweed subjects. A given amount of serum containing "blocking" antibody appeared to "neutralize" a fixed amount of antigen independently of the antigen-antibody ratio of the precipitating mixture. The significance of these observations is discussed.

Robbins, Samuels and Mosko[148] report their chemical studies on a skin reactive fraction from short ragweed pollen, which was prepared by utilizing the following principles: (1) heating at pH 4.0-4.1, (2) adsorption on $Al(OH)_3$ cream, (3) release by a pH 7.4 M/15 phosphate buffer, and (4) precipitation by alcohol at 0° C. The substance obtained by this method is head stable and skin reactive. The substance contains a protein component. Fourteen amino acids were quantitatively determined in fraction AA. The substance contains a carbohydrate component. It is a polysaccharide containing hexose, pentose, hexuronic acid, but no hexosamine. Spectrophotometric analysis in the ultraviolet showed the presence of small amounts of a flavanol pigment. This substance is more skin reactive than whole ragweed pollen solutions of the same nitrogen concentration. The skin-reactive principle is a protein-carbohydrate complex.

Suer[173] reports and discusses a chemical concept of immunity. Isocyanide structure is offered as the chemical characteristic of toxin; an amine derived therefrom, as antitoxins; the amidines resulting from combinations of the two, as immune body. The organic cyanides were likened to carbon dioxide, as the isocyanides were likened to carbon monoxide. Attention was called to several additional reactions of the isocyanides other than those of amines. An isocyanide as antigen, its derived amine as antibody, and the amidine as immune body, were made in the laboratory and tested for toxicity on mice. The outcome confirmed the expected. Chemical tests made upon E. C. Rosenow's streptococcal antigen and antibody gave evidence that the former contains isocyanide, and the latter, amine. A substance with properties typical of an amine hydrochloride, and highly agglutinative, was crystallized from Rosenow's antibody. A short series of simple amine hydrochlorides were tested for antibody properties. Of the group, methylamine and ethanolamine hydrochlorides were found to be less toxic and to exhibit the highest agglutinative power.

B. Campbell[36] reports on the inihibition of anaphylactic shock by acetylsalicylic acid. The author also used Benadryl, which gave good protection against histamine shock but was without effect on anaphylactic shock. He concluded that acetylsalicylic acid is a true anti-anaphylactic drug in that it interferes with the antigen-antibody reaction to prevent or to decrease the untoward results of the challenging dose of antigen.

Serafini and Biozzi[161] studied blood histamine and histamine blood equivalents after physical exercise in normal patients and patients with hay fever. No significant changes of blood histamine were observed in normal subjects after physical exercise. In patients suffering with asthma and hay fever there was an increase of blood

histamine five to ten minutes after physical exercise. The appearance of allergic manifestations after physical exercise in patients suffering from hay fever, together with a definite rise of blood histamine, seems to suggest that blood histamine has a significant role in allergic reactions produced by physical exercise.

STANDARDIZATION

Very little has been added to the standardization of pollen. In general, we agree with Halpin[86] that standardization of pollen is the outstanding challenge to the allergist.

Becker,[14] in his first paper of a series of statistical analyses of standardization of pollen, uses ragweed extracts and the scratch test. By the use of the log-probit method of Bliss, Becker was able to get a valid estimate of the comparative strength of such extracts and an estimate of the error of the assay. The difficulty with this procedure is that it holds only under well-defined conditions. The test doses must be randomized on the arm, and the subjects should be nearly identical in their degree of skin sensitivity. In his second paper, Becker[15] describes a short graphic method of calculating the assay of ragweed pollen extract. The E.D. and the standard error of the two extracts are compared by the method of Miller and Tainer. The difficulty with the validity of this procedure is the number of approximations involved.

Becker et al,[16] in a study of quantitative skin-testing, noted that a relationship exists between the longest diameter of the resultant wheal following endermal injection and the concentration of the solution. They found by their equation that the wheal size had to lie between 4 mm. and 17 mm.. They confirmed their earlier work that there is a decrease in sensitivity directly with the distance down the forearm, and with the rate of decrease, independent of the concentration in the range of concentrations studied. The decrease between the uppermost and lowermost sites is equivalent approximately to a 55 per cent decrease in strength of testing solution. The radial side of the arm was found to be less sensitive than the ulnar side, equivalent to approximately a 50 per cent decrease in strength of the testing solution.

In another paper by these authors,[17] they found that the log-probit method of Bliss and a shorter graphic procedure were applicable to the assay of the direct skin reactivity of ragweed pollen extracts, using the endermal method. While the log-probit method of Bliss proved to be a valid method of assay, the shorter graphic procedure tended to overestimate the assay values and the standard error.

Andrews,[12] continuing his statistical studies in allergy, used Thurstone's method to determine whether patients' sensitivities would group in related characters or families. The hypothesis is that antigens cluster according to different clinically observed allergic complaints. Groupings were obtained which cannot be explained on any simple scheme of basic or common protein.

DIAGNOSIS

Bonnevie[22] discusses the diagnostic and clinical importance of skin tests. He feels that there are three common types; namely, the wheal or urticarial type, the delayed inflammatory type, and the scratch or eczematous epidermis type. It is a worthwhile article because it crystallizes the views on this subject from the eyes of a European.

Salen,[154] also a European, reviewed the entire problem of skin testing and biologic assay.

Walzer and Golan[183] evaluated the electrophoretic method of skin testing. The method was investigated with a special small type electrode, a current density of 0.5 milliamperes, a three-minute exposure and two drops of a 0.1 mg. nitrogen ex-

tract applied to the positive pole. With the above technique, antigen applied at the positive pole produced positive reactions in 86 per cent of the cases as well as 71 per cent who developed reactions simultaneously at the negative pole. With saline solution, no reactions occurred at either pole. When antigen was applied to the negative pole, 33 per cent of the cases developed positive reactions, but none developed simultaneously at the positive pole. The authors did not find electrophoretic skin testing more preferable than the intracutaneous technique.

Hill,[98] reporting on pollen sensitivity in children, found that in 100 asthmatic children, 84 per cent were positive to one or more pollens, and 90 per cent of these reactions had clinical significance. Hill stressed that in asthmatic children, pollen sensitivity is very common. In 100 consecutive cases of respiratory allergy, eighty were asthmatic, and twenty were hay-fever cases, with a high proportion of the children beginning with hay fever, and progressing to pollen asthma. The author stated that in children pollen sensitivity is not of the same degree as in adults, so that they frequently fail to give positive tests to scratch test materials, and that the intracutaneous test will frequently reveal positive tests which the scratch test has failed to reveal. Scratch tests are done as a rule, followed by intracutaneous tests, if the patient has seasonal symptoms with negative scratch tests. In twenty of thirty patients who failed to give positive skin tests by the scratch method, intracutaneous tests gave positive reactions to one or more pollens in fourteen patients. The author states that uncomplicated pollen allergy does not exist in the asthmatic pollen-sensitive child, but that multiple sensitivity is the rule, revealing sensitivities to other inhalant or environmental allergens. Hill[97] investigated food sensitivities in 100 asthmatic children, using twenty-seven food substances. In all, there were 218 positive reactions obtained. Twenty per cent proved clinically significant, 8 per cent had vomiting and hives, and in 72 per cent there were no connections at all.

In twenty-seven spinach skin-test-positive patients, only 2 per cent were able to be clinically correlated. In twenty-five fish skin-test-positive patients, fourteen were proven clinically significant. In twenty-two potato skin-test-positive patients, none were proven clinically significant. In twenty-one egg skin-test-positive patients, eleven were proven clinically significant.

Cohen and Abrams[43] recorded active allergy as a common cause of growth failure. Control of active allergy is accompanied by a corresponding growth repair, provided an adequate diet is present. The use of the Wetzel Grid offers a simple inexpensive and reliable method of detecting early growth failure.

London[116] described the development of a typical case of fall pollenosis in an eighty-three-year-old woman who lived in the same area for the past forty-seven years. Skin tests were positive to ragweed, dust, wheat, flaxseed and grass pollens. Her serum was also capable of giving a positive passive transfer.

Ralph Bowen[24] reports of his experience with hay fever "X" during the year of 1948. Hay fever "X" begins in early April and continues until mid-August in and around the Gulf Coast region. In 1948, the symptoms attributed to this condition were less in their patients, and certain factors associated with hay fever "X" decreased. The fig trees had less molds on them than usual, and the small white citrus fly, which come in through the ordinary screen in great abundance, was an infrequent visitor. These two factors have been investigated as etiological agents and have been proven negative in relation to hay fever "X."

Mitchell, Sivon and Mitchell[133] report the occurance of vulvo-vaginal pruritus associated with hay fever. This condition was noted in eight children between the ages of two to eleven who suffered from ragweed pollenosis. Hyposensitization therapy with ragweed pollen, or removal to a pollen-free environment, was effective in controlling the symptoms. Itching was most intense in the region of the mucocutaneous junction between the vulva and the vagina. The only visible skin changes were those resulting from scratches.

Shulman[163] studied the use of ragweed ointment in determining seasonal variations of ophthalmic sensitivity. This investigation included the study of variation of ophthalmic sensitivity to ragweed pollen before, during, and after treatment with ragweed extracts. Simulating nature, a preparation of whole ragweed pollen in a non-irritating ophthalmic ointment was prepared. One hundred patients were tested 591 times over a two-year period. Treated as well as untreated cases were included. A large percentage of the cases tested showed a rapid diminution of eye sensitivity, concomitant with a rising tolerance of pollen dosage.

Another group of patients showed an initial diminution of eye sensitivity, followed by a fixation of eye sensitivity at a moderately high level. In these cases, pollen dosage was not tolerated above the level of fixation of the ophthalmic sensitivity. A third group of patients showed positive ophthalmic reactions with high dilutions of pollen. Prolonged treatment caused no diminution of ophthalmic sensitivity. In these patients, pollen dosage was poorly tolerated.

Tuft and Blumstein,[177] in studying patients for maximal breathing capacity and breathing reserve, noted in four of twelve hay-fever patients that they showed signs of bronchial constriction.

Lowell and Schiller,[120] studying changes in vital capacity as means of detecting pulmonary action to inhaled aerosolized allergenic extracts in allergic individuals, showed that a reduction in vital capacity followed the inhalation of certain pollens and dust. In some instances, a fall in the vital capacity was observed in the absence of signs of subjective symptoms of asthma. With their limited experience, they indicate that this method may be helpful in diagnosis. The technique has the advantage that pulmonary reactions indistinguishable from spontaneous asthma may be produced and measured under controlled conditions. This method is also valuable in studying the effects of drugs on asthma-like responses.

Curry[50] compared the action of acetyl-beta-methyl choline and histamine on the respiratory tract in normals, in patients with hay fever, and in subjects with bronchial asthma. Mecholyl and histamine caused a slight reduction or increase in the vital capacity of the normal individual; however, in hay-fever patients there was a definite lowering in the vital capacity, especially during the pollen season. Criep,[46] in discussing practical aspects of allergic rhinitis, points out that in addition to the specific factors, the nasal membrane is also affected by climatic conditions, by irritating fumes and chemicals, by emotional factors, by endocrine factors, by the nasal obstructions and infections. He also points out that seasonal allergic rhinitis may be produced not only by pollens but also by spores of certain molds, by rusts and physical agents.

An interesting approach to the subject of vasomotor rhinitis and allergic rhinitis is discussed by McGrath[130] from the homeopathic point of view.

DRUGS

Cohen and VanBergen[45] reported their findings on the pharmacology and clinical experiences with Isuprel. In their hands, this drug has proven an effective agent in the control of the milder asthmatic symptoms.

The Council of Pharmacy and Chemistry[137] reported on Aleudrine sulfate through the activity of the Therapeutic Trials Committee. This compound was first tried clinically in Germany during the last war, and was found to have a profound bronchodilator action in laboratory animals, and unlike epinephrine and ephedrine, to have a vasodilator action. This action was thought so desirable as to warrant thorough investigation of its effects in asthma and other allergic conditions. Preliminary work indicates that it is not as potent an agent in man as is indicated by animal study. Furthermore, when given by intramuscular injection or by mouth in doses sufficient to exert a significant bronchodilator effect, patients may experience typical anginal attacks and show electrocardiographic changes compatable with

coronary constriction. There is some indication that these serious side effects can be mitigated by administering the drug sublingually and by inhalation.

The writers[105a] of this paper have had considerable experience with Aleudrine sulfate (isopropyl-epinephrine), known on the market as Isuprel. Our results corroborate that of the council's report exactly. We wrote that in no way can Isuprel take the place of epinephrine; however, the use of Isuprel sublinqually allows the patients greater ease in controlling minor asthmatic attacks, as well as the bronchospasms associated with coughing in the allergic. We found that the use of Isuprel by mouth or by intramuscular injection led to side reactions that precluded its use. The use of Isuprel by inhalation in the strength of 1:200 was in no way as profound as epinephrine 1:100; however, it is another drug in our armementorium, useful in bronchial asthma. This drug, in our opinion, will find its greatest use through the sublingual route, and secondly, by inhalation. It will definitely be accepted as one of the better sympathomimetic drugs, closely resembling epinephrine, having great bronchodilator effect and less of the pressor effects of epinephrine.

Krasno, Grossman and Ivy[109] investigated the use of "norisodrine" sulfate dust (Aleudrine) by inhalation. In their hands they found that the drug gave complete relief in twenty-four asthmatics. This drug was given in conjunction with some other suitable symptomatic drug. The authors found dizziness and/or palpitation in association with slight tachycardia and a fail of blood pressure in twenty-one of the twenty-four patients.

Herxheimer,[96] writing on the effect of Aleudrine in bronchospasm, says it is effective in relieving attacks of bronchospasm. The drug can be administered sublingually or inhaled. Tolerance to the drug is acquired by some patients. The optimal dosage varies widely in different people and should be determined in every case by spirometry.

Dunlop and Hunter,[58] in attempting to repeat Herxheimer's work, found that they could not agree with him because he did not control his experimental subjects. Herxheimer thinks that the negative results obtained by Dunlop were due to suboptimal doses.

In a note in the *JAMA*[106] the subject of "khellin" is discussed. They state, "That khellin may have further uses is suggested by the observation that after a single intramuscular injection of 200 to 300 mg., complete and prolonged relief was obtained in forty-one of forty-five patients with severe bronchial asthma; and even this fairly large dose had no effect upon the blood pressure. It has, moreover, relieved attacks resistant to adrenaline and aminophylline. Whether, as suggested, khellin is safer than aminophylline is not yet certain, for experience with it is so far small. If, however, khellin is to come into general use, preparations of it must be purified and standardized, for there is some evidence that the impurities in Ammivisnaga may be toxic."

Gilman,[78] in a very excellent article on the pharmacology of drugs used in allergic conditions, discusses them from the theoretical point of view. The theory of chemical mediation with particular reference to the action of acetylcholine and sympathin is outlined. The author points out that the term "antihistaminic" is a poor one since they do not by themselves cause any prominent degree of muscular relaxation or have any effect on the peripheral vasculature in their own right; also, that we are not dealing with physiologic antagonists but with a type of blocking agent. An interesting note by the author is the statement that "the administration of arsenic may in some way be related to the stimulation of the lymphoid and myeloid tissue in the production of antibodies, and may explain the alleged success of Fowler's solution in allergy."

Curry, Fuchs and Leard[51] report their observations, clinical and experimental, with

Orthoxine. Orthoxine (orthomethoxy-beta phenyl-n propyl-methylamine hydrochloride) is a new sympathomimetic compound, which, like ephedrine sulfate, is an active bronchodilator when given by mouth, but in contrast has relatively little pressor or central nervous system simulating effect. In view of the obvious advantages of such a compound in the treatment of bronchial asthma, the following studies were made: In fourteen asthmatic patients, asthma-like attacks with reduction in the vital capacity were induced by the parenteral injection of methacholine and histamine. Orthoxine in 200 mg. doses and ephedrine sulfate in 30 mg. doses were compared by their ability to protect against the reaction to histamine and methacholine according to techniques previously described. Another group of twenty-one patients with bronchial asthma were given Orthoxine and ephedrine sulfate, and clinical response and side reactions were noted. In both groups of patients the effects of Orthoxine and ephedrine sulfate were comparable, but undesirable side reactions were not experienced after Orthoxine. In twenty-four subjects given 100 to 200 mg. of Orthoxine, only two showed a slight elevation in the blood pressure, and tachycardia was not observed in any case. It appears that Orthoxine has a definite place in the management of mild bronchial asthma, since it is an effective bronchodilator, is active when given by mouth, and has relatively little pressor or central nervous stimulating effect.

Wittich,[191] in his report of the "Clinical Evaluation of Orthoxine," said that "it is not affected by digestion, may be given orally, doesn't cause nervousness or central nervous system excitation." It is good for the prevention of reactions which follow the injection of pollen or inhalant extracts, and is best used with barbiturates. It is also useful with synthetic amines such as theophylline, and aminophylline. It is comparatively free of side effects. In 175 patients, the author reports seventy-three good results, sixty fair results, and forty-two poor results.

Simon[165] reports on the use of Nethaphyl. His patients preferred Nethaphyl with phenobarbital, to Amodrine, Tedral or ephedrine with Amytal. The author had good relief without side reactions of tachycardia, palpitation or rise in blood pressure, and nervousness. There were no toxic reactions sufficient for discontinuation of the drug.

SPECIFIC TREATMENT

Very little has been added to the specific treatment of pollenosis. Doyle[55] describes his method of desensitization by way of the nasal mucosa. However, he first uses injections by the intradermal route, and then continues by injecting the nasal mucous membrane, until a dose of 1 c.c. is reached. Local anesthesia of the mucous membrane, with 1 per cent Neo-Synephrine, 1 per cent Privine and 10 per cent Benadryl is used.

Loveless[117] has continued with her adjuvant treatment of hay fever, using emulsions of pollen extracts with fava alba and mineral oil in total doses of 1,000 to 2,000 units. She has been able to go from 1,000 to 7,000 units in two visits. The conjunctival tests, as well as passive transfer tests, are used to determine clinical response as well as the patients' improvement.

Jennes[102] of Connecticut, in a general discussion of the subject, calls attention to the specific therapy of secondary allergies during a hayfever period.

Henson[94] discusses specific treatment of pollenosis from the standpoint of Floridians.

Harley of England[90] discusses preseasonal, as well as coseasonal treatment of hay fever, and includes a discussion of the antihistaminics used in England.

Hansel[88] recommends the coseasonal method of treatment because it is safer, more economical, and gives satisfactory results. The control of non-pollen sensitivity is absolutely necessary in the management of the hay fever patient. In his

series, seventy-one out of seventy-five hay fever cases began before the age of forty, and twice as many males as females under twenty-one were affected. The coseasonal treatment is given by injecting 0.03 to .05 milliliters intracutaneously or subcutaneously.

NONSPECIFIC THERAPY

Schwartz and Leibowitz[157] reported on the clinical evaluation of the topical application of 0.5 per cent isotonic buffered solution of Pyribenzamine Hydrochloride in seasonal and nonseasonal hay-fever patients. In a group of ninety-five patients, complete or partial symptomatic relief occurred in forty-nine out of fifty-nine (83 per cent) of the cases of seasonal hay fever, and in twenty-seven of thirty-six (75 per cent) of the cases of nonseasonal hay fever. No relief was obtained in nineteen cases (20 per cent) in this group. None of the patients experienced any systemic toxic reactions. Thirty-eight (40 per cent) of the group complained of slight burning of the nose. Two patients were unable to tolerate the solution after the first application because of marked burning of the nose and throat. In consideration of the results reported here, and in view of the absence of systemic toxic reactions, 0.5 per cent Pyribenzamine appears to be a valuable antihistaminic drug for topical nasal application in seasonal and nonseasonal hay fever.

Fenton and Huffman[70] reported their results on the use of iontophoresis of Pyribenzamine Hydrochloride in nasal allergy. Twenty patients with seasonal and perennial hay fever were treated by iontophoresis, using a nasal pack saturated with Pyribenzamine in 2 per cent and 5 per cent solutions. Treatments averaged eight minutes to each side of the nose, with the current varying from 3 to 7 milliamperes in intensity; half-wave galvanic current was used. Reactions consisted of slight temporary dizziness in 50 per cent and drowsiness in 20 per cent of the patients. Controls included distilled water or normal saline; treatments were given twice a week. Eight seasonal hay-fever patients, who had not received previous specific therapy, were treated, with excellent results in six cases. Immediate improvement resulted in all instances, lasting eight hours in two, and forty-eight hours in the others. Those with nasal obstruction were especially grateful for the relief obtained. After two or three treatments, these patients were then given specific therapy for the remainder of the season. Eleven cases with perennial hay fever were treated similarly for periods of four to eight weeks; their previous treatment had been of no value. Five cases, or almost one half of the total number, received 75 per cent relief. Two cases relapsed within two weeks, but the remaining six still show some improvement. One person with rhinitis medicamentosa due to Privine was kept comfortable when the nose drops were discontinued. One patient with rhinitis, nasal polyps, and bronchial asthma showed no improvement. Iontophoresis offers a new approach for quick relief in seasonal hay fever, temporary relief in perennial hay fever, and the only relief for the patient who must discontinue nasal vasoconstrictors to which he has become accustomed.

Findeisen[73] treated ninety-six patients with hay fever for three successive seasons with Pervitin (methedrine-N-methyl-B-phenyl-isopropylamine hydrochloride). The average therapeutic dose required was from 9 to 12 mg. daily. Eighty-nine of the patients reported good results with this drug. Unpleasant side reactions included disturbed sleep, headache, palpitation, anorexia, and a diminished sense of well-being, but no serious toxic effects were noted.

Markow, Bloom, and Leibowitz,[125] in a study on the use of Hydryllin, found that of eighty-one cases of asthma and hay fever, 70 per cent of the asthmatic patients, and 52 per cent of the hay fever sufferers showed an improvement. In all other instances the results were poor.

Gutmann[81] stated that vitamins A, C, D and K used in large doses, were ineffective in the treatment of allergic "warm season conjunctivitis." Intramuscular

injections of vitamin B_2 (riboflavin), in 5 mg. doses, were quite effective during the acute stage of the disease, despite the fact that avitaminosis was not present; riboflavin by mouth in no way affected the course of the disease. No explanation for the mechanism of action of riboflavin in vernal catarrh was offered.

The use of 10 per cent argyrol nasal packs was decried in the answer of a query in the *JAMA*,[139] which stated that "the use of mild protein silver packs in allergy is certainly contraindicated. It will lead to chemical irritation of an already irritable, hypersensitive mucosa."

Montreymand[56] discussed the treatment of hay fever, and in addition to specific and nonspecific desensitization, he used antihistaminics as well as gelsemium.

ANTIHISTAMINICS

From perusal of the literature on the antihistaminics it is abundantly clear that enough care has not always been taken to eliminate from the clinical trials those factors which contribute to erroneous clinical impressions. It is likely that herein lies the explanation of the otherwise irreconcilable variation in apparent efficacy of these remedies in the hands of different workers.

Haley[83] presented an excellent review of the antihistaminic drugs in general, giving a summary of the principal actions of histamine, the chemistry of the antihistaminics, their general pharmacology, their action in blocking histamine and their clinical usage. In his summary he stated that the results obtained in asthma and in histamine-induced gastric secretion were disappointing, and indicate that the drugs are not true antihistaminics on the particular body system involved, or that some other agent causes the symptoms attributed to histamine. He felt that the toxic effects of all these drugs are similar, and excessive dosage was dangerous.

Marsh[126] reviewed the pharmacology of the antihistaminics and commented on their mechanism of action, namely, competitive inhibition. These agents do not prevent the allergic response in the body; they prevent only the resultant symptoms (that is, when they are effective at all.) With allergies to known causal agents, avoidance of contact, or gradual desensitization to the allergen, produces much less physiologic unbalance in the body, and much less hazard of undesirable effects. Although no symptoms indicative of chronic toxicity have been observed, he suggested that treatment be continued only eight weeks at a time.

Following are some comparative studies on various antihistaminic drugs.

Aaron and Criep[1] compared the action of Neohetramine and Thephorin. In this study, 243 patients were given Neohetramine and 382 were given Thephorin. They felt that both drugs had good antihistaminic and anti-anaphylactic properties and that they compared favorably with the other histamine antagonists in their clinical value in allergic states. In addition, they exhibited a relatively low incidence of side effects. Toxicity studies were performed on hospitalized patients who received 300 mg. of the two drugs daily, and no significant changes were discernible in the urine, blood pressure and electrocardiographs. However, in two cardiac patients who used Thephorin, the T wave became inverted but returned to normal on discontinuance of the drug. Their report indicated that of the patients who had hay fever and were given Neohetramine, 33 per cent obtained complete relief, 27 per cent moderate relief, 22 per cent slight relief and 18 per cent no relief. The figures on Thephorin were as follows: 44 per cent obtained complete relief, 32 per cent moderate, 14 per cent slight and 10 per cent no change whatsoever. The incidence of side effects was 10 per cent with Neohetramine and 23 per cent with Thephorin.

Kleckner[108] gave a clinical appraisal of three drugs: Benadryl, Pyribenzamine and Anthallan. He felt that Benadryl was the most potent drug of the three in the treatment of seasonal allergic rhinitis. Pyribenzamine, on the other hand, had the

advantage of causing less than one-half the toxic side reactions of Benadryl; he felt that some of the serious side reactions can be quite hazardous. He stated that Anthallan was effective in the treatment of allergic rhinitis, but its outstanding quality was that it elicited no toxic side effects. It was his opinion however, that these drugs were no substitute for an adequate allergic investigation and that their indiscriminate use was to be thoroughly discouraged.

McGavick et al,[128] comparing the toxic manifestations produced by Benadryl and Pyribenzamine, felt that Benadryl produced a preponderance of sensorial disturbances while Pyribenzamine produced mainly gastrointestinal manifestations, and that the incidence of reactions were about equal for the two drugs.

Gay, Landau et al[77] presented their clinical observations on various antihistaminic drugs used on 428 cases of seasonal and perennial allergic rhinitis. The dosage employed was 50 mg. every four to six hours for all the drugs except Antistine, in which case 100 mg. was used, and Hydryllin, where 25 mg. was used. The drugs studied were Pyribenzamine, Hydryllin, Antistine, Neo-Antergan, 1913 (Searle), 1721 (Searle), Histadyl, and Chlorothen. In general, 60 to 76 per cent of the patients were benefited, best results being obtained with Pyribenzamine, Hydryllin, Antistine and Neo-Antergan. Changing from one drug to another produced results equal to, worse than, or better than the original drug. There was no rule as far as one drug being more or less effective than another; this varied from patient to patient. Side effects varied from 13 per cent with Antistine to 42 per cent with 1913 (Searle). Their conclusions from this study were that no parallelism existed between effectiveness against histamine in guinea pigs and effectiveness against human allergy. The wide differences observed in potency with histamine experiments were not found clinically. They felt that it is fortunate that we are able to choose among several preparations and to change from one to another when necessary, but that these drugs cannot replace the diligent search for the etiological factor and its elimination if found.

Arbesman[13] conducted some comparative studies using Pyribenzamine, Hydryllin, Neo-Antergan, Antistine and Neohetramine and reported the following results in extrinsic allergic rhinitis. Eighty per cent were improved on Pyribenzamine with an incidence of side effects of 26 per cent. With Neo-Antergan 63 per cent were improved and side effects occurred in 33 per cent. For Hydryllin the figures were 56 per cent and 35 per cent, for Neohetramine 43 per cent and 16 per cent, and for Antistine 30 per cent and 14 per cent. All of the patients did not use all the drugs, but from the data obtained, Pyribenzamine offered more relief than any of the others. Although Neohetramine and Antistine appeared "less potent," they proved to be the most effective drugs in certain patients, and the incidence of side effects was least with these two drugs, and they could often be tolerated when Pyribenzamine and the others had to be discontinued.

Weiss and Howard[186] compared the effectiveness of Neo-Antergan and Pyribenzamine with other forms of therapy of seasonal allergic rhinitis. They divided their hay-fever patients into six groups. One group received hyposensitization treatments plus placebo, the second and third group received hyposensitization plus one or the other antihistaminic as needed. A fourth and fifth group received placebo injection plus an antihistaminic, and the sixth group was given placebo injections plus placebo tablets. From their figures it would appear that hyposensitization treatment alone was just as effective as such therapy supplemented by Pyribenzamine or Neo-Antergan. However, they felt that this was not exactly true, as when they evaluated their results according to the type of hyposensitization treatment employed, they found that a preponderance of the patients on Pyribenzamine and injection therapy were given coseasonal treatment, which they consider the least effective form. Neo-Antergan was found to produce more side reactions and have slightly less effect in supplementing injection therapy than Pyribenzamine. The anti-

histaminic drugs do not prevent the development of seasonal asthma. They finally concluded that hyposensitization therapy supplemented by antihistaminic medication is the treatment of choice for hay fever.

Waldbott and Young[182] studied the effect of six antihistaminics, namely: Antistine, Neo-Antergan, Neohetramine, 3277 R.P., Trimeton and Benadryl. The drugs were administered only when symptoms were in evidence. They stated that in general it was apparent that the drugs closely resembled one another in the degree and duration of relief afforded; the beneficial effect, when obtained, persisted from four to six hours. However, the action of 3277 R.P. appeared to be decidedly more protracted. They concluded that no decided difference in the efficacy of each individual drug was noted except that the effect of 3277 R.P. appeared to be more protracted than that of the others; the usual side effects occurred and were most pronounced with this drug. However, it would seem to us that the actual figures presented on efficacy belie such conclusions; to use two examples, namely, 62 per cent received marked relief when using Trimeton, and only 28 per cent received the same degree of relief with Neo-Antergan.

Spain and Pflum[167] evaluated the use of various antihistaminic drugs in 2,500 hayfever cases. They felt that 60 to 75 per cent showed improvement, the greatest improvement occurring in those patients with slight or average pollen sensitiveness who were also undergoing hyposensitization. Relief when it came, was usually within a half hour; patients with high degree of sensitivity obtained disappointing results. They felt that there was no prolonged protection and that unpleasant side effects prevented extended treatment when necessary. It was their opinion that this class of drugs should not be used to control constitutional reactions. These drugs are palliative, being in no sense curative, and developing no specific immunity for the patient. In emergencies they are not effective enough to replace epinephrine; even in moderate allergic attacks they are often less satisfactory than epinephrine or ephedrine. Unpleasant side effects occurred in approximately one-third of all cases. There is great variation in individual effect and dosage necessary to produce the effect; these drugs should not be used without supervision. In general, they concluded that the antihistaminics have proven to be most helpful agents against those allergies whose symptoms result from sudden and acute edema, and against many forms of pruritus. They are not intended to replace specific immunizing procedures except possibly in the mildest cases.

A very interesting study was conducted by Holtkamp et al,[99] comparing Benadryl, Pyribenzamine and Hydryllin on the basis of their effect in therapeutic doses on mental ability, reaction time, two-point discrimination distance, pulse rate, blood pressure and respiratory rate. In over one-half of the subjects tested, mental ability, reaction time and minimum distance of two-point discrimination was appreciably altered by these drugs. Pyribenzamine showed a decrease in efficiency in a greater number of individuals than did Benadryl, but the latter occasionally caused decreases of considerably greater magnitude. Hydryllin caused an increased efficiency in a majority of the subjects but adversely affected a few. It would have been highly desirable to have had a larger series of cases upon which these interesting studies were performed.

Serafini,[160] using various histamine antagonists, found that they could modify the histamine tolerance curve in allergic patients. Using Antergan in fifteen hayfever patients, he found that two-thirds of the cases received complete relief and the other one-third were afforded partial relief. This relief was temporary and palliative; side reactions occurred in two cases. It was interesting to note that constitutional reactions in the course of routine hyposensitization therapy disappeared when the drug was given. He felt that his experiments afforded further evidence that histamine plays an important, although not exclusive role in allergic conditions in human beings.

Halpern and Hamburger[85] continued their research on synthetic antihistaminics, reporting this time on Phenergan (3277 R.P.). They administered this drug orally in dosages of 25 to 100 mg. daily (in some cases as high as 200 mg.). Its use in 142 hay-fever patients resulted in complete disappearance of all signs and symptoms in ninety-eight (69 per cent) of them. Partial relief, consisting of cessation of sneezing but not affecting nasal congestion, occurred in thirty-six cases. The eight remaining cases were unaffected, but these patients could not tolerate therapeutic dosages. In the majority of the cases, 25 mg. daily suppressed sneezing, but from four to six times this dose was necessary to give complete relief of all symptoms. Twenty-five per cent of these patients exhibited slight degrees of drowsiness with vertigo and irritability—usually neutralized by Benzedrine; these symptoms usually disappeared when treatment was continued. They felt that the experimental and clinical results indicated that Phenergan was a powerful antiallergic drug. This drug, interestingly enough, influenced several conditions in which no allergic cause could be demonstrated, such as pulmonary edema due to epinephrine or poison gas and orthostatic albuminuria. In consequence, the problem of the mechanism of action of Phenergan still has to be elucidated; their experimental work suggests that this compound acts on capillary permeability. Halpern[84] found that injection of this drug greatly increased capillary resistance in eight of ten patients with allergic conditions, while on the other hand no such result was obtained in nonallergics. It is very striking to note that most of the pathological conditions controlled by Phenergan are characterized by serous extravasation through the capillary wall.

Another of the newer antihistaminics reported upon, was Trimeton. Wittich[190] used this drug on thirty-three hay-fever patients, twenty-five of whom received good results, six fair and two none. The total improved in the pollenosis group was 90 per cent with no side reactions. The most beneficial effects were obtained when used in conjunction with immunization measures and for preventing systemic reactions with high dosage of pollen extracts by administering a 25 mg. tablet about one-half hour before injections.

Ethan Allan Brown[27] used this same drug in 227 patients, of whom 61 per cent became completely symptom-free and 22 per cent received moderate relief. Of those having hay fever, 90 per cent were relieved. Side reactions consisted chiefly of drowsiness in 16 per cent of the patients; 6 per cent had to discontinue the drug because of side effects.

Another new drug that received considerable attention was Decapryn. Brown and Werner,[25] reporting on its pharmacology, demonstrated by laboratory experiments a comparatively low toxicity and potent antagonistic action to the effects of histamine on various tissues. A high degree of antagonistic action follows its use by all routes of administration; cutaneous effects of histamine, as measured by wheal ing reaction in rabbits, were antagonized. It has considerable local anesthetic activity. These same authors[26] also reported that this preparation protected experimental animals against both natural and acquired hypersensitiveness and anaphylaxis.

E. A. Brown, et al[28] studied the effects of this drug on 140 consecutive patients, seventy-one of whom were private cases and sixty-nine clinic cases. The dosage used varied from 6.25 mg. to 150 mg. four times daily, the average being 12.5 to 25 mg. Of the private patients with hay fever, fourteen derived excellent relief, three moderate relief, with slight side effects in one patient. Six patients with asthma and hay fever were relieved of nasal symptoms with no effect on their asthma. In twenty-six clinic patients with hay fever, eighteen obtained excellent relief, six moderate, and two negligible relief. Slight side reactions occurred in three patients, moderate ones in six, and severe in only one. In six patients who had both asthma and nasal symptoms, excellent results were obtained in both nasal and bronchial symptoms in two, excellent as to nasal symptoms alone in one, moderate relief of nasal symptoms in two, and of asthmatic symptoms in one, and negligible results in

another one. Drowsiness of a moderate degree was reported by one, and severe drowsiness by another. In general, 80 per cent of their patients with typical hay-fever symptoms were relieved by Decapryn. Drowsiness was the most commonly encountered side reaction, and was observed in about one patient out of six. The most disturbing side effects were apparent in those taking comparatively high doses. In the 12.5 to 25 mg. dosage range they felt that fewer than 10 per cent occurred. Of those who had previously taken other antihistaminic agents (fifteen had taken Benadryl, seventeen Pyribenzamine and sixteen had had both drugs) one preferred Benadryl, three Pyribenzamine and of the remainder, all but one, who was relieved by none, preferred Decapryn.

Feinberg and Bernstein[68] studied the effects of Decapryn on eighty-one patients with seasonal hay fever due to grasses, ragweed pollens or fungus spores. Some of these patients were untreated while the majority had received previous desensitizing injections. Satisfactory relief was obtained in 62 or 76 per cent of their patients; this relief was temporary. The patients in their series felt that there was a tendency to longer duration with this drug than with other antihistaminics. The dose varied from 12.5 to 50 mg. They found that in some patients a highly soporific effect was obtained with this drug, and therefore large doses should not be prescribed without previous trial on smaller doses. The incidence of side effects encountered was 34 per cent of their total patients, with sedation and sleepiness being the most prominent effects. After six months' trial, no serious or remote toxic effects were manifest. They made note of an important fact reported on by other investigators as well, namely, that in patients with hay-fever asthma, the antihistaminic may relieve the hay fever but *not* the asthma; desensitization is highly effective in the prevention of this type of asthma, and it is obvious that the antihistaminics should not be depended upon in such cases.

Sheldon et al[162] reported on the use of Decapryn by fifty-five patients with hay fever. They subdivided the symptoms exhibited by these cases, giving the results obtained individually. They classified results as satisfactory if there was over 50 per cent relief, and unsatisfactory if relief was less than 50 per cent. Sneezing occurred in forty-one patients, thirty-one of whom obtained satisfactory relief. Rhinorrhea occurred in fifty-four patients, with satisfactory relief being obtained in forty-three. Of thirty-seven who complained of nasal obstruction, twenty-six claimed satisfactory relief. Thirty-one had itching and twenty-seven were relieved; thirteen complained of fatigue, with satisfactory results in eight patients. In 57.2 per cent of these patients, side reactions of drowsiness occurred. The duration of the physiological effect was from four to twenty-four hours after a single dose, and they found no evidence of chronic toxic manifestations. They felt that the beneficial effects from Decapryn would appear to be of a similar magnitude to those reported for Benadryl and Pyribenzamine, but of longer duration.

An antihistaminic, Thephorin, with a radically different chemical structure from that of previous histamine antagonists, received considerable attention. Sternberg and Gottesman[170] used this drug in forty-one hay-fever patients. Eighteen of these had good results, four had fair, and nineteen had no results. All of the subjects were given hyposensitization therapy but were not adequately relieved. They used the drug on a total of seventy-six patients with various allergies, and found side effects in only five of them, all of whom complained of insomnia. They felt that Thephorin is an effective antagonist. They stated that it must not be forgotten, though, that all antihistaminic agents are only palliatives, and none of these preparations will relieve the physician from attempts to recognize the offending allergens, and to eliminate them, or to hyposensitize the patient.

We had a not inconsiderable experience with this drug during its trial stage and feel that this preparation is a useful addition to our armamentarium, especially be-

cause of its stimulating side effects when they do occur, and secondly, for the fact that the incidence of any side effects is usually small.

Frank[74] reported on its use in 140 patients, thirty-seven of whom had hay fever, and thirty-one of these benefited from therapy. Speculum examination proved objectively the shrinking of the congested nasal mucosa, sometimes within one-half hour after the initial dose. As much as 400 mg. daily was tolerated without untoward effects. In general, symptoms were controlled by daily dosage of 50 to 150 mg. Side effects occurred in 38.6 per cent, being severe in 12.8 per cent. Insomnia was the most commonly encountered symptom; excitability was another. In general, the majority of side effects were manifestations of central nervous system stimulation. Reactions were less common in children than in adults.

Criep and Aaron[47] had 180 patients with seasonal hay fever using Thephorin, with 44 per cent reporting complete relief, 32 per cent moderate relief, 14 per cent slight relief and 10 per cent no relief. Many of these patients were receiving concomitant injection therapy. Of the total of 389 patients with various allergic manifestations, that were used in their study, 23 per cent had side reactions. The majority of these were of a stimulant nature or those referable to the gastrointestinal tract. They concluded that this drug was an effective antihistaminic agent both experimentally and clinically. Toxicity studies did not reveal anything of note, and they felt that clinically Thephorin was of as much value as the other antihistaminics in the treatment of allergic states.

A very interesting study was conducted by Boyd et al.[23] Thephorin was given orally to 100 selected nonallergic subjects in daily doses varying from 75 to 700 mg. for periods of one week or more. These patients recorded all symptoms of any nature not present prior to administration of the drug. The most frequently observed unpleasant manifestation of the action of this drug was dryness of the mouth, which occurred in 22 per cent of these patients, being most marked at higher dosage levels. In smaller doses, 300 mg. daily or less, insomnia was the most common manifestation. In all, forty-two of the 100 subjects developed one or more toxic symptoms while taking Thephorin. The use of this drug in the above dosage range for four or more weeks was not associated with any significant changes in electrocardiograms, nonprotein nitrogen, blood count or urine studies. When compared with other drugs that have antihistaminic activity, namely, Benadryl and Pyribenzamine, Thephorin is less toxic weight for weight in daily doses ranging from 150 to 600 mg.

Cohen, Davis and Mowry[44] reported that 105 patients out of 161 who had allergic rhinitis obtained good results using Thephorin; twenty-three had fair; and thirty-three poor results. Of a total of 292 patients who took the drug, fifty-four had side reactions, thirty-three of whom complained of nervousness. Peters[136] described his clinical experiences with Thephorin in 142 cases, sixty-eight having hay fever and thirty-four having both asthma and hay fever. He felt this preparation was effective in 97 per cent of the hay-fever cases. In those patients having both asthma and hay fever it was effective in controlling the symptoms in 91 per cent. This is truly a remarkable record, especially in view of the fact that it is generally accepted that the antihistaminics are ineffective in preventing asthma in those cases of pollenosis of the hay-fever and asthma type. Total side effects reported in the entire group of cases were 11 per cent, and in only five cases were symptoms severe enough to necessitate discontinuance of the drug. The types of side reactions most commonly encountered were insomnia and gastric disturbances.

Lehman[113] reported on his laboratory experiments with Thephorin and felt it to be a potent antihistaminic on isolated guinea pig ileum, in the spray test, against intracardial histamine and against anaphylactic shock; it was also a potent local anesthetic.

Vanderbrook and Olson et al[178] did numerous pharmacologic experiments with Pyrrolazote, another histamine antagonist, and demonstrated it to be a potent antag-

onist to many of the pharmacologic responses of histamine. When compared with Pyribenzamine, it was effective for a longer period and had similar antianaphylactic properties. It appeared to be from one half to one twentieth as toxic as the latter drug. Chronic toxicity studies in rats indicated that it was not harmful.

One hundred and sixty-five patients with seasonal and perennial allergic rhinitis were treated by Waldbott[181] with Neohetramine; 68 per cent were benefited; a little over 10 per cent had side effects, with dizziness and drowsiness being most prominent. He felt that, in general, the results compared favorably with corresponding observations on other antihistaminic drugs.

Bernstein and Feinberg,[18] using the same preparation, reported that 48 per cent of sixty-five patients given 50 mg. doses obtained satisfactory relief, and in thirty patients given 100 mg. doses 70 per cent were satisfactorily relieved. As compared to some of the other antihistaminic compounds, larger doses seemed to be required for therapeutic effect. They felt that with doses producing a reasonable degree and incidence of therapeutic effectiveness, the incidence and degree of side reactions were less than with most other antihistaminic drugs. They felt this drug to be a useful addition because of its apparent low toxicity.

Scudi and Reinhard,[158] commenting on this aspect, found the drug to be about one half as toxic as other antihistamine agents from intraperitoneal toxicity studies in mice.

Criep and Aaron[48] employed Neohetramine in 50 mg. doses every four hours, as necessary, in 124 cases of hay fever; 33 per cent obtained complete relief, 27 per cent moderate, 22 per cent slight, and 18 per cent no relief. Relief when obtained lasted three to six hours. Many of these patients were receiving concomitant hyposensitization therapy, and evaluation was by comparison with periods when the drug was not taken. Side reactions occurred in 10 per cent of their cases; nervousness and palpitation seemed to occur most frequently. They felt that this drug was as effective as the other histamine antagonists, both experimentally and clinically. Toxicity studies on seventeen patients failed to reveal any changes of note.

Alperstein[11] reported on the use of two halogenized ethylenediamine derivatives (Bromothen and Chlorothen) supposedly less toxic and more effective than Pyribenzamine. He used these drugs on twenty-six patients who had experienced side effects from Benadryl and Pyribenzamine and had had to discontinue their use; these were cases of allergic rhinitis and hives. Eighteen of these patients received Chlorothen and eight Bromothen; all of these patients manifested relief in fifteen to thirty minutes with a 50 mg. tablet, and none experienced any side effects. Twenty-five additional patients with various allergic manifestations were given Chlorothen and twenty-two Bromothen; they all obtained relief and none experienced side effects. This was a preliminary report with no protocols and no conclusions except that further investigation was warranted.

We[61a] have had considerable experience with Chlorothen, upon which we reported at the recent meeting of the American College of Allergists, and unfortunately our experiences would not bear out the above glowing report.

The effect of a chemical combination of aminophylline with diphenhydramine—Hydryllin—was reviewed by Brown and Brown.[29] Of eighty-one patients with hay fever, thirty-nine obtained 100 per cent relief, twelve had 75 per cent relief, sixteen had up to 50 per cent relief and fourteen received no beneficial effects. Side reactions, of which drowsiness and dizziness were the most common, occurred in 35 per cent of the patients; because of the severity of these, twenty-one patients had to discontinue its use. However, it was their impression that side effects were notably less with this drug than with diphenhydramine alone. They seemed to get striking relief in pollen asthma. Markow,[125] using the same drug in twenty-seven

patients with hay fever, found that it was beneficial in fourteen of them (52 per cent). Toxic reactions occurred in 37 per cent of his patients, a third of which were severe enough to necessitate discontinuance of the drug.

Levin et al[114] used Antistine and Neo-Antergan in the treatment of hay fever and felt that these drugs were of value in this condition. It was their feeling that Neo-Antergan seemed to have more antihistamine properties, but at the same time gave more toxic reactions than Antistine. The results from the use of the drugs above were not as good as could be obtained with the combination of the drug and pollen hyposensitization. There was, however, only a little better result from the use of the drugs and hyposensitization than from the use of pollen hyposensitization alone. Apparently they felt that hyposensitization was still the method of choice, and the antihistaminic drugs cannot be considered as substitutes. Nonetheless these drugs are of value as adjuvants, in that they help to relieve some of the more severe symptoms, and shorten their duration even if only temporarily. We must never lose sight of the fact that a considerable number of toxic reactions occur, and they felt that, if used judiciously together with orthodox measures, antihistaminics were a valuable addition to our methods of treatment. In general, Antistine afforded relief in about 65 per cent of their patients with hay fever, and Neo-Antergan in about 70 per cent of the cases. Toxic reactions occurred in 36 per cent of the patients on Neo-Antergan and in 21 per cent of those using Antistine.

Southwell[166] used Neo-Antergan in fifteen patients with hay fever due to grass or grass and tree pollens. They were graded numerically according to the severity of their symptoms: grade 4, severe; grade 3, moderate; grade 2, slight, and grade 1, no symptoms. He used placebos interchangeably with the drug itself, the dose of the drug being 3 tablets (.1 gm.) three times daily. The severity of the hay fever symptoms while taking the drug was a figure of 1.5, whereas while on placebo medication the figure was 3.7. His impressions were, that the hay-fever symptoms were partially or completely controlled by Neo-Antergan and that the patients were unanimous in their praise of the preparation, and felt that they got better relief only from the most successful desensitization course. Side effects occurred in over 50 per cent of the cases; most of these were mild.

Calder[35] used Neo-Antergan in six hay-fever patients, with complete cessation of attacks in five, and slight symptoms only in the other one.

The dosage employed was 0.2 gm. three times daily until the end of the pollen season. He was of the opinion that this drug was an effective antihistaminic, but like all of these preparations it does not cure and must be given for as long as an effect is desired. When treatment is stopped, there is a quick relapse of the patient's condition. It was his feeling that desensitization remains the treatment of choice, and the antihistamine drugs should be used only where the offending antigen cannot be found, or pending desensitization. In this total series of cases (including thirty-eight with vasomotor rhinitis), mild side effects occurred in four. It is well to remember that clinical evaluation can be difficult since allergic manifestations are frequently self-limiting, and in chronic conditions spontaneous improvement may take place at any time, because of the sudden disappearance of certain inhaled or injected antigens or by spontaneous desensitization.

Winter et al[188] performed some chronic toxicity studies with Neo-Antergan in animals; the drug was administered to various animals for varying lengths of time up to six months. No toxic signs or abnormalities were found in these animals with the dose employed. They concluded that there was no evidence that this drug had any cumulative effect at small and moderate doses.

In two cases of tree pollen allergy, Hughes[101] used Antistine with complete control of symptoms in both. Each had notable conjunctival symptoms and both were satisfactorily relieved by Antistine-Privine eye drops. He also used the drug in several cases of preseasonal ragweed and grass hyposensitization therapy for the

prevention and control of reactions, and it appeared to be of value in allowing more freedom from reaction. His incidence of side reactions in treating forty-eight patients with various allergic complaints was 12.5 per cent.

Kaplan and Ehrlich[104] found that Antistine afforded some measure of relief in a majority of hay-fever patients to whom it was given. Such results were less evident, but still present, in many with perennial allergic rhinitis. The drug was very efficacious in children, because adequate dosage could be given with minimal side effects.

Friedlander and Friedlander[75] felt that Antistine produced some degree of symptomatic relief in 59 per cent of patients with allergic rhinitis. The effect on rhinorrhea and sneezing appeared to be greater than on nasal blockage. In those patients who had also used Pyribenzamine, a comparison between the two in the same patients indicated a greater effect on the part of Pyribenzamine in most instances, while a smaller percentage found Antistine superior. Side effects from Antistine were generally less frequent than with Pyribenzamine. In many instances those unable to tolerate Pyribenzamine could take Antistine in effective doses without side effects.

Linadryl, used by McGavack[128] in fifty hay-fever patients in a dosage range of 150 to 400 mg. daily, resulted in complete relief in twelve patients, some improvement in eight more, and no relief in thirty (60 per cent) of the patients. Of a total of 250 patients with all types of allergic manifestations, side effects were manifested in a little over 17 per cent. None became apparent until 250 mg. or more of the drug was taken daily; a tolerance frequently developed as the drug was continued. By far, the commonest complaint was drowsiness. They concluded that Linadryl has an action similar in nature to that of Benadryl but is probably less than one-half as effective, weight for weight; and if the dose were pushed to a point of comparable effectiveness in every case, it would probably cause an equally high number of unpleasant symptoms.

Intravenous Benadryl was given by Mackmull[123] to fifty patients in doses of 50 to 300 mg., and various systemic reactions were encountered, but none of sufficient severity to require treatment. Average systolic and diastolic blood pressures were elevated with large dosages. He felt that such intravenous doses of Benadryl were contraindicated in the presence of hypertension. Electrocardiographic changes of sufficient significance occurred after 200 to 300 mg. doses. The results of the experimental work of Chen et al[38] indicate that the joint antihistaminic effect of Adrenalin and Benadryl is additive, while the joint lethal toxicity of the two at low dosages of Benadryl Hydrochloride is synergistic in nature.

Preliminary studies conducted by investigators of NMRI[49] suggest that the toxic effects of Benadryl are such that piloting of aircraft during the course of the drug's action may be hazardous. In Queries and Minor Notes,[141] the question of the use of Benadryl and Pyribenzamine during pregnancy was asked. The query stated that the patient in question had taken these drugs during a previous ragweed season while pregnant and had aborted. The answer given was that, thus far, reports had not indicated that these drugs produced abortion. They further stated that if drug sensitivity existed, drug sickness might ensue which might have some undesirable effect in pregnancy.

Tomlinson[176] writes that at the end of the hay-fever season he saw two similar cases that he felt suggested a possible changed allergic state. Both patients were females who were given Benadryl (150 mg. daily) for their hay-fever symptoms, with complete suppression of these symptoms. After taking the drug for the season, they both presented an eczematous eruption of the face, neck and forearms, and with local therapy the eruption subsided. It occurred to him that the suppressive action of Benadryl may have transferred the reactions from the nasal mucous membranes to the skin. It would seem to us that aside from the theoretical implications involved,

certain other explanations would need to be invoked; for example, evidence that this may or may not have been a toxic side reaction.

Sachs[153] reported a patient who used 600 mg. of Benadryl daily and developed many untoward symptoms including hallucinations and jerky rapid speech. He then presented an excellent review of the literature on the subject of side reactions with the use of this drug, reporting such reactions in 46.4 per cent of 1210 patients. Drowsiness was the most frequently encountered toxic reaction. When the mode of administration is by vein, toxic reactions are more frequent, occurring in 65 per cent of forty-three patients; these reactions were more acute in onset, more severe and of shorter duration. Weakness was seen much more frequently when the drug was given intravenously. The untoward reactions that occurred were classified as (1) neuropsychiatric, (2) alimentary, (3) cardiovascular, (4) respiratory, (5) genito-urinary, (6) muscular, (7) ocular, (8) miscellaneous (pruritus, aggravation of allergic symptoms). The mechanism of toxic reactions has not been adequately explained except in those cases of sensitivity to acetylsalicylic acid (both drugs having a coal tar radical). These toxic side reactions are most common with higher doses; however, profound reactions have occurred following a single dose, and 600 mg. daily have been given without any. Toxic reactions occur on some occasions in the same patient on the same dosage while not at other times. It is not possible to correlate the dose level with the type of reactions. The occurrence of toxic effects may be minimized by reducing the dose, taking the drug after meals, using the initial dose in the evening, and prescribing stimulants. A large number of patients developed tolerance, and the side effects disappeared. Within several hours after discontinuance of the drug, in those cases of toxic effects, the manifestations usually disappear, and there is no evidence of any cumulative toxic effect.

Starr and Rankin[168] noted a child of eighteen months of age who had taken three to five 50 mg. capsules of Benadryl and developed convulsions, cyanosis and bulging eyes within a half hour. Upon admission to the hospital the child was comatose, threshing wildly about, with marked erythema of the face and extremities, dilated pupils that did not react to light, bilateral nystagmus and frequent toxic convulsions. He was treated by gavage with instillation of 6 c.c. of magnesium sulfate solution, 10 c.c. of phenobarbital and 75 mg. of Sodium Amytal intravenously. Gradual improvement took place in twenty-four hours. It might be interesting to note at this point, that with lethal doses in animals, death is preceded by excitement and convulsions. Blackman et al[20] reported a case of exacerbation of acute bronchial asthma following Benadryl therapy, terminating in a fatal outcome. The authors admit however, that the case in question cannot categorically be considered as due directly or entirely to Benadryl. The primary cause of death appeared to be severe central nervous system depression.

Brown[31] made a controlled study of side reactions to Pyribenzamine on patients who were receiving injections of typhoid vaccine. Forty-eight patients were given five 50 mg. tablets in twenty-four hours (some patients were used two to three times so that the total was 100 times). On fifty-six occasions, the dose of Pyribenzamine was doubled in thirty-seven patients. Nervousness, dryness of the mouth and headache were more frequent in the control group as compared to the 50 mg. Pyribenzamine group. Drowsiness, nausea, dizziness and insomnia were less frequent, but nonetheless quite evident, in the control group. All of the above side reactions were more frequent when the dose of Pyribenzamine was doubled. These data indicate that the 50 mg. dose of Pyribenzamine, which is the most frequently used dose, has a negligible effect in producing the stated symptoms, all of which have been ascribed to Pyribenzamine medication. These data indicate the importance of using controlled studies in evaluating the side reactions as well as the therapeutic effects of a new drug.

Fanburg[64] described a case of fever, secondary to Pyribenzamine medication.

Following discontinuance of this drug, the patient's temperature returned to normal. Subsequently this drug was readministered, with an abrupt onset of pyrexia, followed by an abrupt termination on discontinuance of the medication; this would seem to indicate that the drug was responsible for the fever.

The mode of action of antihistaminic agents was studied on atropinized guinea pig ileum by Alonso et al,[10] and their results indicated that the law of mass action was obeyed over a thousand-fold concentration range of both histamine and antagonist. The drugs studied were Benadryl, Pyribenzamine, Neo-Antergan and Chlorothen. They concluded that these results were in agreement with the theory that histamine and the above antagonists compete for the same cellular receptors. Rense[146] compared the action of histamine and antagonists on isolated organs in various ways as to their power to antagonize histamine, and his results showed that Neo-Antergan was first, 3277 R.P. second, Benadryl third, Antistine fourth, and Nupercaine last. He was of the opinion that of the five drugs employed in these studies, Neo-Antergan was the most specific; also that the activity of these drugs as local anesthetics appeared to be more nearly related to their activity against acetylcholine than to their activity against histamine.

Comparative studies of antihistaminic substances were made by Landau and Gay[111] by means of Dale tests, and they found three groups of potencies. The most highly potent were Neo-Antergan, Pyribenzamine, Chlorothen, Promothen and Histadyl. Of moderate potency were Benadryl, 1721 (Searle), and 3277 R.P., with Antistine being in the weakest group. However, one must not lose sight of the fact that it is well known that laboratory experiments of this type are not directly transposable clinically.

Winter[189] conducted experiments with guinea pigs and mice, using several antihistaminics together with barbiturates. Pyribenzamine, Benadryl, Neo-Antergan and 3277 R.P. were the preparations employed. He found that the potentiating effect of Benadryl upon the sedative action of these barbiturates was much greater than that of Neo-Antergan or Pyribenzamine. However, all the drugs employed prolonged the sleep-producing effects of barbiturates. These results appear to correlate with the reported incidence of sedation as a side effect in patients receiving antihistamine drugs.

Stavraky,[169] using ferrous sulfate by mouth in daily doses of 20 to 45 grains in conjunction with Pyribenzamine or Antistine, felt that the combination was most effective in alleviating allergic manifestations in eight patients with ragweed hay fever and asthma. Iron also seemed to relieve lassitude and drowsiness induced by antihistamine agents, making possible increases in doses of Pyribenzamine and Antistine with further benefit to the patient. As a precautionary measure, the iron was given with calcium to decrease the toxicity of the former substance. This highly interesting study would be more informative with a larger, more well-controlled series of patients.

After several years of trial with the various antihistaminic agents, it would seem apparent that most men would subscribe to the following conclusions: It must not be forgotten that all antihistaminic drugs are only palliatives. None of these preparations will relieve the physician from attempts to recognize the offending allergens and to eliminate them if possible, or to hyposensitize the patients to them. These drugs have a place *in conjunction* with the orthodox therapy when the latter does not adequately control the symptoms, or before that therapy brings relief to the patient.

MISCELLANEOUS

Rockwell[149] described eighteen synthesized derivatives of histamine and treated two cases of hay fever with no results. He pointed out that the therapeutic results of histamine therapy, when they are obtained, may be due to its pharmacological

action *per se* and not to the induction of any increased tolerance to histamine; he also noted that such preparation may be effective orally. Krueger[110] treated forty-one cases of allergic rhinitis with histamine acid phosphate on an ambulatory basis, and concluded that, in general, the results were poor, with twenty-seven failures, eleven cases improved, and only three with good results. A query in *JAMA*[143] was put as to whether any contraindication existed to the use of Hapamine and one of the antihistamine drugs. The answer was that if antibodies were produced (which is debatable) as a result of histamine-azo protein injections, the use of antihistaminics would not prevent their development.

This, of course, is also applicable to specific hyposensitization; in fact, as reported last year, there is a possibility of a greater production, since it may allow the use of larger doses of the allergen in question.

In an editorial appearing in the ANNALS OF ALLERGY,[60] the possible dangers arising from constitutional reactions, occurring following a shocking dose of pollen extracts, are discussed. Castburg and Schwartz reported important changes in the electrocardiogram. In each case, changes typical of anoxemia of the myocardium were noted.

Seltzer[159] noted convulsions following an injection of epinephrine in a twenty-six-year-old white man with asthma and rhinitis. The seizures lasted about thirty minutes and were of a general tonic and clonic type. Following injection of five minums of Adrenalin, the rate and depth of respiration increased until there was marked hyperventilation, which was followed by a convulsive seizure. It appeared that the convulsions were associated with a form of hyperventilation and tetany.

J. H. Black,[19] in a discussion of the effect of respiratory allergy upon the life and health of individuals, stated that pollen hay fever is of little significance so far as life expectancy is concerned. Asthma is a frequent sequel of hay fever which becomes perennial.

Fabricant and Perlstein[63] studied the hydrogen ion concentration of nasal secretions *in situ*, for infants and children, and noted that normal nasal secretion *in situ* has a pH ranging from 5 to 6.7; in those with acute rhinitis, 7 to 8; while in subsiding rhinitis the pH drops to 6.7 or to 7.2. In active allergic rhinitis the pH is from 7.2 to 7.3, while in subsiding allergic rhinitis the pH drops to 6.7. It is supposed that normal nasal secretion possesses the purposeful acid barrier against growth of pathogenic bacteria. The authors suggested that pediatric nasal medication possesses a pH value within the range of 5 to 6.7.

In the Queries and Minor Notes of *JAMA*,[140] a question was asked as to the value of air conditioning in pollen allergy. The consultant who answered discussed the results of Rappaport, Nelson and Welker, who found that the results from air filtration with or without cooling are unfortunately disappointing as regards asthma. The symptoms of pollenosis are completely relieved while in the room, but recur in fifteen to forty-five minutes after the patient leaves the room. The symptoms require residence in an air-filtered room for several days before relief is obtained, and asthma will recur if the patient is exposed to pollen for a very short period subsequently. Therefore, it is necessary for the patient to remain in the air-filtered room constantly to afford good relief from pollenosis and asthma. Patients who respond to hyposensitization will be much more comfortable and will be free of residual symptoms if the sleeping quarters are free from pollen.

PSYCHODYNAMICS

We have noted with interest the increase in the number of articles dealing with psychosomatic aspects of hay fever and asthma. Abramson,[3] in his article "Psychosomatic Aspects of Hay Fever and Asthma," points out that early observers in the 18th century called attention to type of symptoms associated with the blooming of the rose. The first type was associated *not* with the presence of the rose,

but actually with the time of blooming of the rose. These observations are as true today as they were then; first, specific relationship to an allergen, and secondly, incidents associated with the time the allergen is present, not necessarily specific in itself. Abramson, whose scientific acumen cannot be questioned, believes in a closer co-operation between men associated with psychosomatic medicine and allergies, and also the need of systematic postgraduate instruction in psychodynamics.

Clark[40] points out that allergy plays an important part in childhood neuroses; therefore, a problem child can be an allergic.

Haiman[82] calls attention to the fact that before success can be gained in treating an allergic person, his personality should be considered, and an insight into his problems evaluated in the light of his allergic treatments.

Miller and Baruch[131] call attention to a study of psychosomatic factors affecting allergies, including hay fever. Evidence of maternal rejection in sixty-two out of sixty-three clinical allergies is noted, as well as over-protection in thirty-six children.

Mitchell, Curran, and Myers,[132] in a study involving an analysis of recorded history interviews, with reference to personality factors in allergic nasal disorders, noted statements revealing feelings of confusion, conflict, hostility, rejection of self by others, social maladjustment, escape, dependency, fear or unhappiness.

Schutzbank,[156] in explaining the influence of climatotherapy for allergic diseases, associated possible psychosomatic influence on patients that have been relieved by change of climate; also a change of climate eliminates offending allergens.

Shure and Harris,[164] in their article, "The Neuropsychiatric Factor In Allergic Diseases," point out that in addition to the allergic factors, emotional states and psychic stimuli are introduced as integral parts of every case. The adoption of the term "intrinsic" for the neuropsychiatric factors, and "extrinsic" for the organic factors in the production of allergic disease is suggested.

REVIEWS

Salmon,[155] in a general review of the "Present Aspects of Allergy," said, "To know allergy is to know medicine." This is becoming ever apparent. Burnet[33] of Australia, in his article, "The Basis of Allergic Disease," reviews the generally accepted concepts of allergy, as related to hay fever. A number of other writers have included hay fever in their excellent reviews. Harley[91] of Australia writes with special reference to aural manifestations; Burrage,[34] with reference to new types of therapy; Lowell,[119] with emphasis on avoidance of constitutional reactions; Sutherland[174] of Australia, with special reference to the nose. The membership of the New Jersey Allergy Society[92] report in their state journal a panel discussion of the entire problem. Matas[127] of Brazil, in reviewing the results of pollen therapy, followed the generally accepted North American ideas on this subject.

NEW BOOKS

This year's outstanding book, dealing with this subject matter is Vaughan's[199] "Practice of Allergy," second edition, which has been completely revised and rewritten by Black. Harold Abramson[194] in his book, "Psychodynamics and the Allergic Patient," has a chapter on the psychosomatic aspects of hay fever and asthma prior to 1900. This was very interesting reading, showing that physicians were aware of emotional factors long before "psychosomatics" became popular. Other books dealing with the hay fever subject are: Gasio and Collicelli,[197] "T'asmo bronchiale dal punto d vista neuro-vegetatino;" Pulay and Lansel,[198] "Constitutional Medicine, Endocrinology and Allergy;" Boscolo,[195] "Asma e catarri costituzionali," and Vintinnre and Marrill,[200] "Hay Fever Studies in New Hampshire, 1947."

Forman's compendium,[196] "Directory of Physicians Interested in Allergy," lists a great number of physicians interested in this subject and should prove very useful to those whose patients move or travel.

A new journal, "Acta Allergologica"[5] on the general subject of allergy is very interesting and should prove helpful in bringing us in closer contact with the north countries of Europe.

Those who have recently become interested in allergy, and want to acquaint themselves with an excellent short history of hay fever, should read Clarke's[39] "The Beginnings of Allergy; a Reminiscence."

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SENSITIVITY TO KELCOLOID

(Continued from Page 682)

individuals without an allergic history and without a familial background of allergy. Kelcoloid is apparently a preparation of low allergenicity, but clinical sensitivity has been demonstrated.

SUMMARY

Although human hypersensitivity, together with the production of allergic symptoms, can occur with Kelcoloid, it must be assumed to have a minor place among the substances responsible for allergic manifestations. It is probably, therefore, a good substitute for such preparations as the water-soluble gums, namely, karaya, locust bean, acacia, tragacanth and Irish moss extract.

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News Items

HANSEL FOUNDATION

The Hansel Foundation held a panel discussion on Friday, October 7, just preceding the annual meeting of the American Academy of Ophthalmology and Otolaryngology at the Palmer House, October 9-14. Dr. French K. Hansel was the moderator, and the program of the panel discussion was as follows:

Morning Session—9:00 A.M.

I. OTOLARYNGOLOGIC DIAGNOSIS OF ALLERGY.

1. Office Management.....W. Byron Black, M.D., Kansas City, Mo.
2. Symptomatology and Manifestations. Edward King, M.D., Los Angeles, Calif.
3. Cytology.....William H. Craddock, M.D., Cincinnati, Ohio
4. Pathologic Changes on the Tissue. X-Ray Diagnosis.....
.....Geo. E. Shambaugh, Jr., M.D., Chicago, Ill.

II. THE ALLERGIC INVESTIGATION.

1. Etiologic Factors.....F. Lambert McGannon, M.D., Lakewood, Ohio
2. History Taking in Allergy.....Joseph W. Hampsey, M.D., Pittsburgh, Pa.
3. Skin Testing.....Geo. E. Shambaugh, Jr., M.D., Chicago, Ill.
4. Prophylaxis—Avoidance or Elimination of Allergens.....
.....Eugene L. Derlacki, M.D., Chicago, Ill.

III. TREATMENT.

1. Disposition of Patient, Plan of Treatment.....
.....French K. Hansel, M.D., St. Louis, Mo.
2. Dust Therapy.....Rea E. Ashley, M.D., San Francisco, Calif.
3. Pollen Therapy.....Michael H. Barone, M.D., Buffalo, N. Y.

Luncheon—12:00 Noon

Afternoon Session—2:00 P.M.

IV. TREATMENT (Continued)

1. Dietary Manipulation and Nutrition.....
.....A. G. Rawlins, M.D., San Francisco, Calif.
2. Drugs.....Walter E. Owen, M.D., Peoria, Ill.
3. Indications for Surgery.....Kenneth L. Craft, M.D., Indianapolis, Ind.

V. HEADACHES, VERTIGO, ALLERGY OF THE EAR.

1. Histaminic Cephalgia.....French K. Hansel, M.D., St. Louis, Mo.
2. Tinnitus.....Howard P. House, M.D., Los Angeles, Calif.
3. Allergy and Deafness.....Hugh A. Kuhn, M.D., Hammond, Ind.
4. Summary of Allergy and the Ear....Gösta Dohlman, M.D., Lund, Sweden

VI. OCULAR ALLERGY.

1. General Considerations.....W. Byron Black, M.D., Kansas City, Mo.
2. Allergic Conjunctivitis and Contact Dermatitis.....
.....S. Albert Hanser, M.D., St. Louis, Mo.
3. Industrial Ocular Allergy.....Hedwig S. Kuhn, M.D., Hammond, Ind.
4. Ocular Allergy.....Wm. D. Gill, M.D., San Antonio, Texas

POSTGRADUATE COURSES IN ALLERGY

Columbia University announces three postgraduate courses in allergy during 1949-50, as follows:

Mt. Sinai Hospital

Medicine PM 36—Allergy. October 4-November 29, 1949; and January 24-March 27, 1950, omitting February 22. Fee $40. *J. Harkavy,* M.D. and staff.

Tuesday 9-11

Fundamentals of anaphylaxis and its relation to clinical manifestations of allergy. Newer concepts of mechanisms involved in hay fever and bronchial asthma and treatment. Food allergy and its effects on the respiratory, nervous, gastro-intestinal, and cutaneous organs. Bacterial, drug and serum hypersensitiveness.

Pediatrics PM 31—Allergy in Children. October 14-December 2, 1949. Fee $30. *M. M. Peshkin,* M.D.

Friday, 3:30-5:30

Anaphylaxis; allergy; asthma, skin and ophthalmic tests. Eczema and angioneuroses.

Roosevelt Hospital

Medicine PM 81—Clinical Allergy. October 17-28, 1949. Fee $120. *Robert A. Cooke,* M.D. and staff.

Monday through Friday, 9-1, and 2-6

This course is designed to provide internists, pediatricians, and other physicians a review of modern concepts of the theoretical and practical aspects of allergy, in relation to clinical problems. All types of allergic disease will be studied including the less common vascular and cerebral allergies. The practical work will include history taking, physical examination, skin testing by direct and passive transfer methods, and laboratory diagnosis. In the laboratory the principles of allergic extractions and standardizations and the preparation of individual extracts will be considered in a practical way. There will also be demonstrations of anaphylaxis, Dale reactions, precipitin tests, and preparation of autogenous vaccines. Maximum class, 8; minimum, 6.

SYMPOSIUM ON DERMATOLOGIC ALLERGY

An important Symposium on Itching Dermatoses will be the highlight of the program of the Sixth Annual Convention of the College from 2:00 p.m. to 5:50 p.m., Tuesday, January 17, 1950, in the Gold Room of the New Hotel Jefferson, St. Louis, Missouri. Dr. Stephan Epstein, Marshfield Clinic, Marshfield, Wisconsin, is chairman of this section. Dr. Stephen Rothman, Professor of Dermatology, University of Chicago, is the guest speaker and will present "The Physiology and Pharmacology of Pruritus." Dr. Carl Laymon, Clinical Professor of Dermatology, University of Minnesota, will discuss "The Diagnosis of Non-Allergic Itching Dermatoses." Dr. F. W. Lynch, Clinical Professor of Dermatology, University of Minnesota, will present "The Classification of Eczema, and the Psychosomatic Factors in Eczema." "The Topical Treatment of Acute and Chronic Dermatitis (Contact and Atopic), Including Antihistamanics" will be given by Dr. James Webster, Assistant Professor of Dermatology, Northwestern University. Doctor Epstein will discuss "The Treatment of Infectious Eczematoid Dermatitis," and Dr. Herbert Rattner, Associate Professor of Dermatology and Syphilology, Northwestern University, "The Treatment of Pruritus." Following a short recess, there will be a one-hour round table panel on "Itching Dermatoses" by Doctors Laymon, Lynch, Rattner, Rothman, Webster and Epstein. All dermatologists are daily encountering allergic skin disorders and they should take advantage of this great opportunity to increase their knowledge of these conditions which are of increasing importance.

BRAZILIAN SOCIETY OF ALLERGY

The ordinary meeting of the Brazilian Society of Allergy was held in conjunction with the Brazilian Society of Dermatology at the Geral Polyclinic of Rio de Janeiro on May 31, 1949. The following program was presented: (1) Conference by Prof. Francisco A. Rabelo, "Dermatologic Manifestations in Allergy." (2) Members of the two societies presented cases. At the ordinary meeting held on June 28, 1949, the following roundtable discussion was held: (1) "Etiology of Asthma" by Dr. Mario Miranda, (2) "Treatment of Asthma" by Dr. A. Oliveira Lima. These two items were followed by a discussion.

SPANISH SOCIETY OF ALLERGY

At the first Congress of the Sociedad Espanola de Alergia at Madrid, which was announced in the May-June issue of ANNALS OF ALLERGY, the Society, by action of the Congress will be known as the Spanish-Portuguese Society of Allergy. Until organized in Portugal, however, it will continue as the Sociedad Espanola de Alergia. It was also unanimously voted to accept the invitation to become an official member of the International Association of Allergists. Dr. Fred W. Wittich was one of the Honorary Members elected at this Congress. Officers elected were: President, Prof. C. Jiménez Díaz; Vice President, Dr. Francisco J. Farrerons-Co.; Secretary, Dr. Iahoz Marques; Vice Secretary, Dr. Iahoz Navarro. Other members elected to the Board were: Prof. Diaz Rubio, Cruz Auñon, Ortiz de Landazuri, Dr. R. Frouchtman, Dr. Sanchez Cuenca, and Dr. Surinyach.

The next Congress will be held in the spring of 1951 at a place to be decided later by the Board of Directors. The following assignments were made: "Influence of Climate on Allergy" to Prof. Cruz Auñon and Prof. Diaz Rubio and Dr. Farrerons; "Beginning of Asthma and its Prophylaxis" to Dr. Sanchez Cuenco; "Allergic Personality" to Prof. Ortiz de Landazuri; "Urticaria" to Dr. Frouchtman, and "Digestive-Allergy" to Dr. Surinyach.

SWISS SOCIETY OF ALLERGY

It is a pleasure to announce the formation of the Swiss Society of Allergy (Schweizerische Allergie-Gesellschaft / Société Suisse d'Allergie). A founder's group of forty-six met on July 16 at Berne, adopted the proposed by-laws, and decided to hold the first annual meeting February 25 and 26, 1950, at Zurich. Officers of the Society, which now has 150 members, are as follows: President, Prof. Dr. A. S. Grumbach; Secretary, P.D. Dr. H. Storck; Treasurer, Prof. Dr. W. Jadassohn; 1st Assessor, Prof. Dr. W. C. Loeffler; 2nd Assessor, Prof. Dr. K. Bucher. This first assembly unanimously accepted the formal invitation of the Executive Committee of the International Association of Allergists to become an official member. This is the sixteenth of the existing twenty-four national allergy societies to become an official member of the International Association of Allergists.

The American College of Allergists extends greetings and sincere congratulations on the organization of this Swiss Society of Allergy which has some of the most outstanding scientists of international reputation in Switzerland as its officers.

AMERICAN ACADEMY OF ALLERGY

The American Academy of Allergy will hold its sixth annual meeting at the Biltmore Hotel, Los Angeles, California, March 6, 7, and 8, 1950. All members of the College who are members of the Academy are urged to attend this meeting which promises to be one of its best. If you are not a member of the Academy, please write to the Biltmore Hotel for a hotel reservation card. If you plan to attend, it would be appreciated if you would notify the Executive Headquarters of the American Academy of Allergy, 208 E. Wisconsin Avenue, Milwaukee 2, Wisconsin.

OMAHA MID-WEST CLINICAL SOCIETY

The Omaha Mid-West Clinical Society held its seventeenth annual clinical assembly October 24 to 28, 1949, at the Hotel Paxton, Omaha, Nebraska. The Society is limited in membership to 155 Omaha physicians who are on the teaching staff of either Creighton University or the University of Nebraska College of Medicine. Its purpose is to offer postgraduate courses for practicing physicians in the midwestern territory. A panel discussion on allergy was presented on Friday, October 28. Dr. J. Harvey Black of Dallas, Texas, Dr. Theodore L. Squier of Milwaukee, Wisconsin, and Dr. Fred W. Wittich of Minneapolis, Minnesota, were guest speakers at this panel discussion.

THE PITTSBURGH ALLERGY SOCIETY

The fall program of The Pittsburgh Allergy Society opened with a meeting on September 19, 1949, at the Women's Hospital, Pittsburgh, Pennsylvania. The guest speaker was Dr. John Mitchell of Columbus, Ohio, who discussed the following subject: Psychogenic Influences in Allergy. There was a large attendance which included representatives from hospital social service departments.

* * *

ANNALS OF ALLERGY, 7:155-300 (March-April) 1949, was indexed under Current Medical Literature of the JAMA 141:153 (September 10) 1949 issue. The article by Rapaport and Peshkin, "Immunity to Diphtheria Induced by Booster Dose of Alcohol-Refined, Alum-Precipitated Toxoids: Based on Study of Fifty-Nine Allergic Children", and "Oral Pollen Absorption: Demonstrated by Controlled Passive Transfer Tests" by Feinblatt and Lové were abstracted.

* * *

Dr. Leon Unger has returned from a trip to Great Britain and Ireland. While there, he addressed the British Medical Association at Harrogate on "Nasal Allergy"; the British Association of Allergists at Cardiff, Wales, and the Institute of Microbiology in London on the subject of "Bronchial Asthma"; and the Association of Hospitals in Oxford on the subject of "Migraine".

* * *

Dr. Herbert J. Rinkel, Kansas City, Missouri, a member of the Board of Regents of the College, presented a talk before the Polyclinic of the Hospital for Sick Children in Paris on the morning of June 30. This was by invitation of Professor Robert Debre, Professor of the Medical Clinic for Children. A lecture was also given before the service of the Hospital Staff, Interns and Medical Service of Doctor Lamay, on July 2.

* * *

Allergists who are consulted by surgeons for skin irritations caused by wearing rubber gloves will be interested to know that the B. F. Goodrich Company of Akron, Ohio, after an extensive investigation, has created a glove which when worn by a number of those who had been sufferers from dermatitis has relieved the skin irritation, according to their personal reports. These gloves are now on the market as "Special Purpose" surgeons' gloves.

* * *

Appointment of R. J. Buckman, M.D., to the medical staff of the sales and promotion division of Parke, Davis & Company, Detroit, Michigan, has been announced by H. J. Loynd, Vice President of the Company in charge of Sales and Promotion.

* * *

Albert V. Stoesser, M.D., F.A.C.A., announces the association of Lloyd S. Nelson, M.D., in the practice of allergy and diseases of children at 1409 Willow Street, Minneapolis, Minnesota.

BOOK REVIEWS

THE MICROSCOPE. Its Theory and Applications. By J. H. Wredden, F.R.M.S., Bedford, with a Historical Introduction by W. E. Watson-Baker, A.Inst.P., F.L.S., F.R.M.A., and a Foreword by R. K. Fleming. 296 pages, 298 illustrations. Price, $5.50. New York: Grune & Stratton, 1948.

This most interesting, profusely illustrated book on the use of The Microscope should be read by every physician who uses this instrument. All allergists can profit very much from the information presented herein.

The excellently illustrated Historical Introduction presenting the discovery and development of the lenses up to the devolpment of the compact microscope is worth the price of the book alone.

Apparently, the object of the author was not only to provide general information about the theory and construction of the microscope, but, as he states, "also to set down a number of more unorthodox applications and processes which I have developed as a result of constant use of the instrument."

There is probably no instrument in science today with such an expanding popularity as The Microscope. The author dwells in great detail on the underlying theoretical principles governing the functioning and mechanical construction of the instrument Although the book is primarily intended for those who are studying Microscopy for the first time, it is also designed for those who have had previous experience with the capabilities of the instrument and who wish to make a serious study of it.

The first two chapters are devoted to optical principles which are presented in an attractive and easily understood manner with diagrammatic illustrations. The instrument is then comprehensively treated part by part in succeeding chapters, with discussions in detail of the functions of the eyepiece, objective, condenser, stand, et cetera. Standard applications of the instrument are dealt with by the author who believes that if the basic principles are easily grasped at the outset, then future work with the instrument, when applying optical principles to any particular problem, will be a real pleasure and open up numerous avenues of information.

The author succeeded very well in covering a very wide field within the scope of one volume on The Microscope in a manner which is simple but yet should be of great interest to those interested in newer methods and processes.

The advantages of binocular microscopes are presented in detail as well as the use of the microscope in photography. The final chapters present the use of the microtome, embedding methods, mounting, et cetera.

The Appendix presents various tables of "Refractive Indices of Various Substances," the "Index of Visibility," and "Dispersions of Glasses," as well as equivalent tables for various measures, constants useful to the microscopist, conversion tables of microns to fractions of an inch, and charts on logarithms and anti-logarithms.

The photographs throughout the book are excellent and really works of art.

PROGRESS IN ALLERGY, VOL. II. Edited by Paul Kallós, M.D., Helsingborg, Sweden. 356 pages, 50 illustrations, 37 tables. Price $7.50. Basel: S. Karger, Publisher, 1949. Interscience Publishers, Inc., New York, Agent for the Western Hemisphere. The contributors to Volume II are: Harold A. Abramson, New York; K. Bucher, Basel; Robert A. Cooke, New York; French K. Hansel, St. Louis; Holger Haxthausen, Copenhagen; Elvin A. Kabat, New York; L. Kallós-Deffner, Helsingborg; Foster Kennedy, New York; Hjalmer Koch, Stockholm; Rolf Meier, Basel; Frank A. Simon, Louisville; Lewis Stevenson, New York; George L. Waldbott, Detroit; and Fred W. Wittich, Minneapolis.

The first volume of "Progress in the Science of Allergy—Fortschritte der Allergielehre" appeared before the outbreak of World War II. It is now out of print and because of many popular demands, Volume II has made its appearance. In the present volume, the author recognizes the rapid development in the field of allergy and its theoretical and practical importance. In this volume, as in the former, the principle of publishing "individual contributions covering some special domains in research or clinic" has been adhered to. In an effort to give equal emphasis to theoretical and practical problems, Doctor Kallós devoted a larger part of both of these volumes to pathology, pharmacology and immunology in the broadest sense. The present volume reflects the development in the whole field of allergy in representing various unhindered opinions. There is an excellent introduction by the editor, correlating observations of the various editors. Throughout the book, authors were selected who were pioneers in their field.

The chapter on "Immunochemistry" by Kabat is one of the most concise and complete reviews of immunochemical investigations including the more recently developed quantitative procedures. His chapter alone has 341 references.

The chapter by Wittich on "Allergic Diseases in Animals" has fifty-five references. This chapter offers the first convincing proof of spontaneous allergy (atopy) in the lower animal manifested by typical seasonal hay fever in a dog established by skin tests, passive transfers, to a dog of a different species and to the human skin, positive nasal and ophthalmic tests, as well as successful hyposensitization and the demonstration of thermostable antibodies by means of the passive transfer and precipitin method.

The reactions and results of bronchoscopic therapy in asthma is fully presented by Waldbott. He also has a very practical chapter on "An Etiological Survey of Chronic Urticaria."

There is a chapter beautifully illustrated on "Present Status of Aerosol Therapy of the Lungs and Bronchi" by Abramson, who, during World War II, pioneered in the field of aerosol stabilization and therapy. When an officer on the staff of the Technical Division, Office of the Chief, Chemical Warfare Service, Lt. Col. H. A. Abramson directed the first investigation on the study of penicillin aerosols in animals and man with a view to utilizing this technique in the treatment of lung infections of all types. This investigation was carried on at Cold Spring Harbor. The work of this author formed the groundwork structure from which our present-day knowledge of aerosol therapy stems. The chapter is complete in details and contains seventy-four references.

There are two chapters by Hansel. He places cytological studies of nasal secretions on a practical basis in the chapter on "The Diagnosis and Treatment of Allergy of the Nose and Paranasal Sinuses." He also has a chapter on the use of "Small Dosage Dust and Pollen Therapy." To review this book without describing some of these authoritative chapters in detail would be unfair.

Professor H. Koch of Stockholm has a chapter on "Allergy in the Middle Ear" which is complete and authoritative. The most interesting syndrome complexes are now recognized as being due to hypersensitiveness. Professor Koch has a more elaborate presentation on the subject in *Acta Oto-laryngologica*, from the Oto-laryngologic Clinic in Lund.

Professor Holger Haxthausen of Copenhagen presents the most recent observations on the striking allergic skin lesions—urticaria, atopic dermatitis, and the allergic eczemas of the contact type. The author has also presented his observations on allergic phenomena, his own observations on various diseases of the skin which he finds to be of topical interest and classifies some of the manifestations of allergy. The bibliography is most complete.

Frank Simon has a chapter on "Allergy to Human Dander in Infantile Eczema."

Foster Kennedy writes in his characteristic inimitable style on "Allergy of the

Nervous System with Especial Reference to Migraine." There is an Addendum to this chapter by Robert Cooke on "The Basis for Allergy in Diseases of the Nervous System."

A brief chapter on "Allergy as a Cause or a Mechanism in Disseminated Sclerosis" by Stevenson is most opportune.

Von R. Meier and K. Bucher present a complete chapter in German on the pharmacology of the antihistaminics which includes grouping of the various formulas showing their relationship and a comparison of their clinical reactions. With the exhaustless literature written on this subject, it is refreshing to absorb so much valuable information on the antihistaminic antagonists presented so simply in one chapter. There are 187 references.

Finally, the editor and Liselotte Kallós-Deffner have a most complete chapter in German on the clinical use of the histamine antagonists. This includes a report on the influence of Antistine on the histamine skin reactions and the clinical results of the use of this antihistaminic on allergic diseases, particularly acute and chronic urticaria and those urticarias resulting from thermo reactions, angioneurotic edema, neurodermatitis, serum sickness, insect bites, the itching dermatoses, Ménière's disease, histamine headaches, migraine, experimental headaches, allergic nonseasonal rhinitis, hay fever, bronchial asthma, diagnostic skin examinations and histamine antagonists, side effects, with a summary of clinical results obtained in the various allergic diseases with the use of Antistine. This chapter is an example of the thoroughness by which a review should be made and is refreshing when compared with some of the fragmentary reports on some of the antihistaminics which now appear in the literature. In fact, the whole text is characterized by a thoroughness of observations on the subject that is most refreshing.

The publishers are to be congratulated on the paper stock and the illustrations. All physicians in allergy could read this second volume to advantage.

ALLERGY IN RELATION TO OTOLARYNGOLOGY. By French K. Hansel, M.D. 77 pages. 6 colored plates. 2 tables. Price $2.50. Saint Paul: Bruce Publishing Co., 1949.

This small compact volume, an official publication of The American College of Allergists, represents a panel discussion on allergy in relation to otolaryngology which was presented at the Fourth Annual Meeting of The American College of Allergists. Dr. French Hansel, chairman of the panel, presents the opening article detailing succinctly the various procedures necessary for the diagnosing of allergy as encountered by the otolaryngologist. This includes symptomatology, rhinoscopic examination, cytology of the secretions, x-ray examination, bacteriology, pathology, general clinical history, examination and laboratory findings.

There are six colored plates illustrating various grades of eosinophilia as well as a table interpreting the cytologic picture, representing combined allergy and infection.

There is a panel discussion by authoritative allergists who present the various phases of diagnosis and treatment including a discussion of psychosomatic influences.

The book is completed with a section on questions and answers following the panel discussion. There is an excellent reference list.

This is the first compilation on the subject of allergy in relation to otolaryngology and emphasizes the necessity of a close cooperation between the otolaryngologist and the allergist when insuring adequate treatment to the patient. All students of otolaryngology or physicians treating ear, nose and throat diseases can read this little book with profit when applying allergy to their specialty.

Important Announcement

The QUARTERLY REVIEW OF ALLERGY AND APPLIED IMMUNOLOGY, the first comprehensive review of allergy and applied immunology, is now published under the auspices of the American College of Allergists. The June and September issues will appear under one cover and launches the *Review* under a new owner and publisher.

The Editorial Board has been completely reorganized. Outstanding allergists and immunologists in various parts of the world are on the Contributing Editorial staff, thus making the *Review* international in scope.

Arrangements have been made to have the details of printing the publication handled by the Bruce Publishing Company of Saint Paul, publishers of ANNALS OF ALLERGY.

Every effort will be made to embrace in the *Review* the highest grade literature on allergy and applied immunology. Instead of mere abstracts, there will be concise, critical accounts of the publications reviewed. Authors are invited to review their own articles.

Classification of subject matter has been greatly simplified. At the end of each year there will be a title and author index which will represent selected reviews on every phase of allergy appearing in the world's literature.

The *Reviews* will be greatly enlarged. The domestic subscription rate for those who are now subscribers to ANNALS OF ALLERGY will be $5 per year and the rate for non-subscribers to the ANNALS will be $6 per year. Foreign postage will be $1.50 additional. Prepaid subscriptions now in effect will be honored at the rate and on basis paid. The subscription rate is so reasonable that no physician applying allergy to his practice can afford to be without the QUARTERLY REVIEW OF ALLERGY AND APPLIED IMMUNOLOGY.

FRED W. WITTICH, M.D.
Editor and Publisher

All orders for subscriptions or renewals should be addressed to the *Quarterly Review of Allergy and Applied Immunology*, in care of the Publication Office, 2642 University Avenue, Saint Paul 4, Minnesota.